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THE PHTHALEIN TEST

AN EXPERIMENTAL AND CLINICAL STUDY OF PHENOLSULPHONEPHTHALEIN IN RELATION TO RENAL FUNCTION IN HEALTH AND DISEASE *

L. G. ROWNTREE, M.D., AND J. T. GERAGHTY, M.D.
BALTIMORE

Phenolsulphonephthalein, which was first described by Remsen,[1] is a bright red crystalline powder, somewhat soluble in water and alcohol and readily soluble in the presence of alkalies. The drug, as determined by Abel and Rowntree,[2] is *non-toxic, non-irritant* locally, and is excreted practically entirely by the kidneys and with extraordinary rapidity, appearing in the urine normally within a few minutes of injection. In alkaline solution it presents a brilliant red color which is ideally adapted for quantitative colorimetric estimation.

TECHNIC

In our earliest work only the time of appearance, the time of maximum intensity of excretion, and the time of gross elimination were considered. In the course of the work it became evident that the color properties of this substance make it peculiarly well adapted for colorimetric methods of estimation, and for this purpose the Duboscq colorimeter was employed and has proved of the greatest value.

In order to obtain data of real value it is essential to any functional test to know, not only the time of appearance of the drug in the urine, but exactly what part of the drug, a known amount of which has been administered, is recovered in a definite period of time.

Twenty minutes to half an hour before administering the test, the patient is given 200 to 400 c.c. of water in order to insure free urinary secretion, otherwise delayed time of appearance may be due to lack of secretion.

Under aseptic precautions a catheter is introduced into the bladder and the bladder completely emptied. Noting the time, 1 c.c. of a carefully prepared solution[3] of the phenolsulphonephthalein containing 6 mg.

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*From the Pharmacological Laboratory of the Johns Hopkins University and the Genito-Urinary and Medical Clinics of the Johns Hopkins Hospital.

1. Remsen: Am. Chem. Jour., 1884, vi, 280.

2. Abel and Rowntree: Jour. Pharm. and Exper. Therap., 1909, i, 231.

3. This solution is obtained as follows: 0.6 gm. of phenolsulphonephthalein and 0.84 c.c. of double normal sodium hydroxid solution are diluted with 0.75 per cent. sodium chlorid solution up to 100 c.c. This gives the mono-sodium or acid salt, which is red in color and which is slightly irritant locally when injected. It is necessary, therefore, to add 0.15 c.c. more of the twice normal hydroxid, a quantity sufficient to change the color to a beautiful Bordeaux red. This preparation is non-irritant.

to the c.c. is accurately administered subcutaneously, intramuscularly or intravenously by means of an accurately graduated syringe.[4]

The urine is allowed to drain into a test-tube in which has been placed a drop of 25 per cent. sodium hydroxid solution and the time of the appearance of the first faint pinkish tinge is noted.

In patients without urinary obstruction the catheter is withdrawn at the time of the appearance of the drug in the urine, and the patient is instructed to void into a receptacle at the end of one hour and into a second receptacle at the end of the second hour.

A rough estimate of the time of appearance can be made by having the patient void urine at frequent intervals without the use of the catheter. In prostate cases it is wise to have the catheter in place until the end of the observation. The catheter is corked at the time of the appearance of the drug in the urine and the cork is removed at the end of the first hour and at the end of the second hour, the bladder being thoroughly drained each time. On many of the patients of this type on whom our observations have been made, a retention catheter has been in use as part of the routine treatment on account of the residual urine. When a catheter is to be employed it is well previously to have the patient under the influence of hexamethylenamin.

Each sample of urine is measured and the specific gravity taken. Sufficient sodium hydroxid (25 per cent.) is added to make the urine decidedly alkaline in order to elicit the maximum color. The color displayed in the acid urine is yellow or orange, and this immediately gives place to a brilliant purple-red color when the solution becomes alkaline. This solution is now placed in a liter measuring-flask and distilled water added to make accurately 1 liter. The solution is then thoroughly mixed and a small filtered portion taken to compare with the standard, which is used for all of these estimations.

In our earlier work the amount of drug excreted was estimated by means of the Dubosc q colorimeter, the technic of which has been described in our original publication.*

Recently the Autenrieth-Königsberger colorimeter[5] has been modified by us and utilized for the quantitative estimation of phthalein. A standard alkaline solution, 6 mg. of phthalein to the liter, is placed in the wedge-shaped cup. The urine, collected as for the other method, is diluted to a liter and a small filtered portion poured into the rectangular cup. The wedge-shaped cup is now manipulated by means of the screw until the two sides of color field are identical in intensity. The percentage is now read directly by the position of the indicator on the scale.

4. We have used the Record 2 c.c. syringe which is graduated in fifths of a c.c.

5. This instrument is manufactured by Hellige in Freiberg; our modification can be obtained from Hynson and Westcott, Baltimore, Md.

*Jour. Pharm. and Exper. Therap., 1909.

This instrument is well adapted for the purpose, is approximately accurate, and is much cheaper than the Duboscq colorimeter.

Fairly accurate estimations, however, can be obtained by means of graduated cylinders—equal quantities of the standard solution and the diluted urine being used in separate cylinders and the denser solution being diluted until the colors become identical. The amount of drug in the solution being known, the amount in the urine can be readily calculated.

When the collected urine has been made strongly alkaline it is necessary to estimate the phthalein within a few hours as the red color fades gradually under these conditions. When it is desirable or necessary to defer the estimation for some hours or days, it is better to make the urine distinctly acid, under which condition the phthalein remains unchanged. It should of course be made alkaline again when the estimation is made.

The method heretofore utilized in connection with other tests, of determining the time necessary for total elimination, is erroneous for the following reason: Whereas in the case of phthalein, a normal kidney excretes the greater part of the dye injected within two hours of the time of its administration, and then only a small trace for the next two hours, the moderately diseased kidney secretes a fair amount within the first two hours, say 50 per cent. of that excreted by the normal kidney, but the concentration in the blood still being high it continues to excrete a fair amount in the following two hours, so that at the end of four hours little difference may exist in the total work accomplished. One-hour and at most two-hour observations are therefore recommended. In cases in which only slight changes in function exist this can be most accurately demonstrated by one-hour collection following the use of an intramuscular (lumbar) injection.

THE INFLUENCE OF THE RÔLE OF ABSORPTION ON THE RATE OF EXCRETION

It must be admitted that a factor other than renal excretion, viz., absorption, enters in consideration in connection with the test when the phthalein is administered subcutaneously or intramuscularly. Obviously, a considerable error is introduced from the standpoint of absorption in the use of the subcutaneous method, when factors, such as edema, which may modify the rate of absorption, exist. On this account the excretion in health following different methods of administration has been studied in some detail.

INTRAMUSCULAR AND SUBCUTANEOUS ABSORPTION OF SULPHONEPHTHALEIN

Meltzer and Auer[6] were the first to demonstrate that absorption from the intramuscular tissue is much more rapid than that from the subcuta-

6. Meltzer and Auer: Jour. Exper. Med., 1905, vii, 59.

neous tissues. They worked with epinephrin, curare, fluorescin and morphin, and demonstrated beyond doubt that these substances found their way into the general circulation much more rapidly when the injections are made into the muscles. Patta[7] was unable to detect any rise of blood-pressure following the intramuscular injection of epinephrin and concluded that the results obtained by Meltzer and Auer[6] were in reality due to intravenous injections. Wallace,[8] working with epinephrin, obtained results identical with those of Meltzer and Auer, but also felt that the results were dependent on tearing of the veins and were in reality intravenous injections. Joseph and Meltzer,[9] in their work in relation to physostigmin in poisoning by magnesia salts, again demonstrated intramuscular absorption to be far superior to subcutaneous. Auer and Meltzer,[10] by methods used with specific intention of detecting whether the rapidity of intramuscular absorption was dependent on the tearing of veins during the injections or to the direct insertion of the needle into a muscle vein, proved satisfactorily that such accidents were not responsible for the rapidity of absorption, but that rapid absorption occurs through the walls of the blood-vessels of the muscles. In the same communication they also asserted that absorption from the lumbar is much superior to that from the gluteal muscles.

Phenolsulphonephthalein, by virtue of the properties whereby it is rapidly and quantitatively excreted by the kidney, furnished an excellent method of studying this problem. An investigation into the comparative quantitative excretion of phenolsulphonephthalein following these two methods of administration was consequently undertaken.

The first experiments were carried out on bitches. The time of appearance of the drug in the urine following subcutaneous administration of 1 c.c. of phthalein solution (6 mg.) and the quantitative output of phthalein for periods of varying lengths were determined. The lumbar muscles of these dogs were then exposed by a small incision, direct intramuscular injection made, and the time of appearance of the drug in the urine and the quantitative output for corresponding periods again determined. Finally, intravenous injections were given and similar observations were again made.

The time of appearance was determined as follows: A catheter was passed into the bladder and then 1 c.c. of sulphonephthalein was injected subcutaneously, intramuscularly or intravenously. The bladder was then injected at 30-second and one-minute intervals with small quantities of warm sterile boric solution and this was immediately drained into flasks

7. Patta: Arch. ital. de biol., 1906, xlvi, 463.
8. Wallace: Med. Rec., 1907, lxxi, 876.
9. Joseph and Meltzer: Jour. Pharm. and Exper. Therap., 1909, i, 369.
10. Auer and Meltzer: Jour. Exper. Med., 1911, xiii, 328.

containing a few drops of sodium hydroxid. The first appearance of phthalein in the washings was noted and the amount of drug excreted for the varying periods was then determined.

The results obtained from these observations appear in Table 1, from a study of which it will be seen that the time before appearance is shortest for the intravenous and that the drug appears much more rapidly (3.5 to 7 min.) following an intramuscular than following a subcutaneous injection (5.5 to 12 minutes). The amount of excretion is dependent on the amount of absorption, the kidney function not playing a rôle inasmuch as the same dogs were used throughout for these

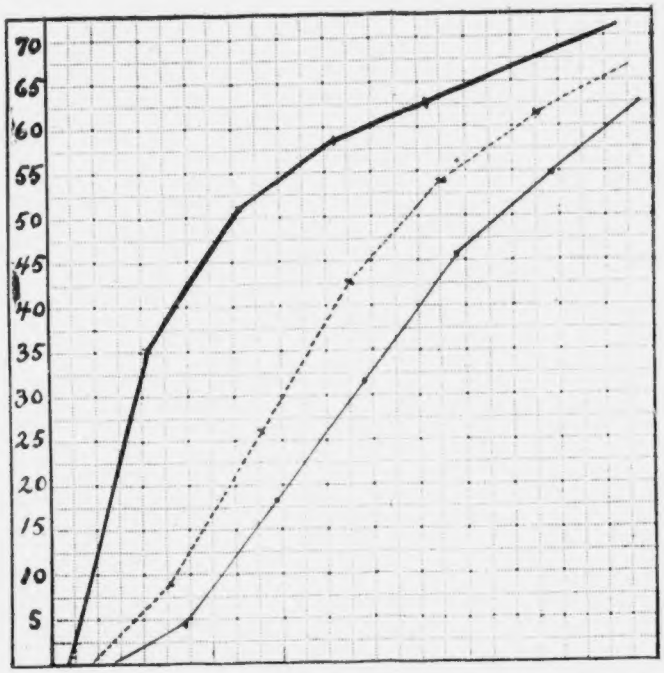

Chart 1.—Curve of excretion in a dog for one hour, estimations being made at ten-minute intervals. Upper black line represents the excretion after intravenous, the dotted line after intramuscular (lumbar) and lower black line after the subcutaneous administration.

experiments, the kidney function being therefore approximately the same. It appears that the absorption for one hour from the subcutaneous tissues averages from 5 to 10 per cent. less than that from the intramuscular, while at the same time considerable variation (37 to 62.8 per cent.) exists in the absorption for the same dog (Dog 5, Table 1). The absorption from the intramuscular tissue for one hour appears to display less variation (58.8-68 per cent.), but the absorption is not absolutely complete, as

the excretion for one hour is somewhat less than that following intravenous injections.

The difference, however, in the absorption from these two methods of administration is much more striking when one-half hour observations are taken—over twice as much absorption following intramuscular injections as compared with subcutaneous (Dogs 4 and 5, Table 1). This suggested to us the idea of the necessity of comparing the curve of excretion in order to obtain the real difference in the rate of absorption. Estimations were made at ten-minute intervals following injections by all three methods of administration. A comparison of the excretion in one dog (No. 5, Table 1) is indicated in Chart 1. A similar comparison for the excretion in man following intravenous, lumbar, gluteal and subcutaneous administration is shown in Chart 2.

TABLE 1.—COMPARISON OF EXCRETION OF PHTHALEIN IN DOGS FOLLOWING INTRAVENOUS, INTRAMUSCULAR (LUMBAR), AND SUBCUTANEOUS ADMINISTRATION

	Time of Appearance			Amount 1st ½ Hour			Amount 1 Hour		
	Subcut.	Intramus.	Intraven.	Subcut.	Intramus.	Intraven.	Subcut.	Intramus.	Intraven.
Dog 1	..	5	1½	....	....	54.9	57.4	66.7	....
	..	5	2	....	....	54.6	65.	58.5	62.5
	..	7	....	....	....	....	50.	55.6	....
	8	....	....	....	....	....	50.	....	....
	10	....	....	....	....	....	50.5	....	....
Dog 2	..	7	2	....	....	....	48.	50.	....
	..	4½	....	....	....	....	63.	58.8	....
	..	6	....	....	....	....	47.7	55.5	....
	10	....	....	....	....	....	47.7	....	....
	11	....	....	....	....	....	55.5	....	....
	7	....	....	....	....	....	50.	....	....
Dog 3	..	3½	2	....	....	50.9	37.6	52.6	64.
	12	5	....	....	....	....	41.7	61.7	....
	7	5½	....	....	....	....	43.5	....	....
	7	(*)	....	....	....	....	37.9	....	....
Dog 4	..	6	....	....	....	....	45.9	....	....
(Pregnant)	7	4½	....	....	....	....	53.8	64.	....
	8	6	....	....	....	....	50.	....	....
	8	4	..	10.9	26.3	....	....	....	....
	5½	4½	....	10.	22.4	....	....	....	....
	6	3½	....	10.	45.4	....	....	....	....
Dog 5	..	5	2	....	....	58.3	50.	64.9	71.3
	8½	5	....	....	....	....	37.	58.8	....
	7	5	....	20.	....	....	62.8	68.	....
	8	4	....	17.7	51.	....	....	66.6	....
	..	5½	....	....	45.8	....	....	....	....

(*) Not read.

EXCRETION IN NORMAL INDIVIDUALS AND VARIATIONS DEPENDENT ON METHODS OF ADMINISTRATION

The excretion has been studied in several hundred normal individuals. In our earlier work subcutaneous administration was used exclusively,

the drug appearing in the urine in from five to eleven minutes, 40 to 60 per cent. (average 50 per cent.) being excreted in the first hour after its appearance in the urine, and 60 to 85 per cent. for two hours. In health the elimination is practically completed in two hours, only a trace being present during the third and fourth hours.

On account of the large variations in excretion in normal individuals following subcutaneous administration, it was thought a large part of this variation might be due to tardiness of absorption. The excretion following intramuscular (gluteal and lumbar) injection was consequently investigated. After gluteal injection (thirteen readings in twelve individuals) variations from 41.7 to 62.5 per cent. were encountered (Table 1) for one-hour readings (ten minutes being allowed for time of appearance), an average of 51 per cent. being eliminated.

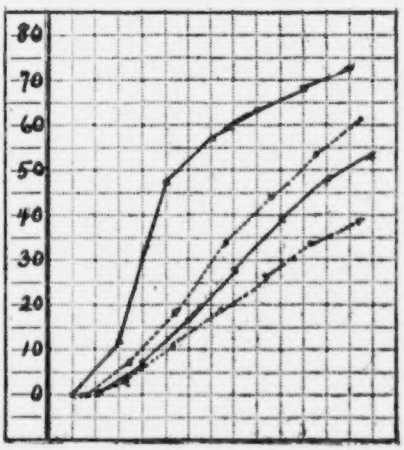

Chart 2.—Curve of excretion in a man for one hour, estimations being made at ten-minute intervals. Upper black line represents excretion following intravenous injection; upper dotted line, excretion following lumbar injection; lower black line excretion following gluteal injection, and the lower dotted line represents excretion following subcutaneous injection.

In twenty-one readings on fourteen normal individuals the variation following lumbar injection (Table 2) was from 51.8 per cent. to 64.1 per cent., except in Case 10, in which the first test read 40.2 per cent., and there being some doubt as to the accuracy of the technic, three subsequent control injections were given showing an output of from 60 to 61 per cent. on each occasion. The average output of the twenty readings was 57.5 per cent. This would seem to indicate *that absorption plays but a small rôle in affecting the accuracy of the test when one-hour determinations following intralumbar injections are employed.*

TABLE 2.—INTRAMUSCULAR INJECTION: LUMBAR

Case	Time of Appearance, Minutes	——Percentage Excreted—— 1st Half Hour	2nd Half Hour	1 Hour
1. G.	8	35.7	16.1	51.8
2. D.	6	19.2	35.7	54.9
3. O.	6	45.8	16.6	62.4
4. S.	7	32.5	21.8	54.3
5. G.	7	32.3	26.3	58.6
6. M.	..	32.3	21.7	54.
	..	33.3	21.	54.3
7. Y.	7	26.3	26.3	52.6
8. N.	6	33.3	29.8	63.1
9. J.	8	29.	25.	54.
10. M.	7	23.	17.2	40.2
	8	....	....	60.9
	..	....	....	60.5
	..	....	....	60.2
11. S.	6	....	....	61.7
	.	....	....	64.1
	7	38.8	24.4	63.2
12. G.	8	....	....	51.8
13. R.	5	....	....	62.5
	..	....	....	62.5
14. G.	8	34.	26.2	60.2
Average				57.4

TABLE 3.—INTRAVENOUS INJECTION IN NORMAL CASES

Case	Time of Appearance, Minutes	——Percentage Excreted—— 1st Half Hour	2nd Half Hour	1 Hour
1. U.	5	56.8	23.3	80.1
2. L. C.	4	53.2	10.8	64.
3. S. B.	4	66.6	13.4	80.
4. K.	?	....	....	70.
5. S.	3½	....	....	62.5
	4	....	....	62.5
	4	....	....	63.3
6. D.	4	....	....	70.
7. L.	..	58.8	13.2	72.
8. C.	..	64.1	13.8	77.9
9. S.	*	46.7	11.1	57.8
10. J.	..	55.5	9.	64.5
	..	62.5	10.2	72.7
11. P.	6½	....	....	66.6
12. M.	4	....	....	62.5
	..	....	....	65.8
	..	....	....	65.5
13. S.	4	....	....	62.5
14. Y.	4	....	....	71.5
	..	....	....	68.5
Average				67.9

*Question as to being normal.

Intravenous injections have been employed (Table 3) with three ideas in view, namely, in order to determine, first, the total excretion for one hour; second, what variations in kidney function existed in normal individuals; and third, to what extent absorption was responsible for variations in excretion. The output for one hour (twenty readings in

fourteen individuals) averaged 67.9 per cent., considerably higher than that from other methods of administration. The excretion varied from 62.5 to 80 per cent., with one exception, No. 9, who excreted 57.8 per cent. This individual gave a somewhat low output following all methods of administration, although no other evidence of renal disease could be discovered.

Table 4 shows the variations in percentage excretion for one-hour periods in the same individuals following subcutaneous, gluteal, lumbar and intravenous administration.

TABLE 4.—EXCRETION IN NORMAL INDIVIDUALS FOLLOWING FOUR DIFFERENT METHODS OF ADMINISTRATION

Case		Subcut. 1 hr. %	Intramus. gluteal 1 hr. %	Intramuscular lumbar 1-2 half hr. %	Intramuscular lumbar 2nd half hr. %	Intramuscular lumbar total for 1 hr. %	Intravenous 1st half hr. %	Intravenous 2nd half hr. %	Intravenous total for 1 hr. %
1	C.	53.2	62.5	....	....	....	64.1	13.8	77.9
2.	L.	....	58.9	....	....	....	58.8	13.2	72.
3.	S	35.7	47.6				46.7	11.1	57.8
4	S	52.6	53.7						62.5
									62.5
									63.
5	S. B.	38.8					66.6	13.4	80
6	U.	41.6	49.				56.8	23.3	80.1
7.	M								62.5
		43.1	43.4	32.3	21.7	54.			65.8
		58.8	....	33.3	21.	54.3			65.5
8.	S.	42.7	47.6						62.5
9.	Y.	60.9	41.7	26.3	26.3	52.6			71.5
		44.3							68.5
		45.5							
10.	B.	42.	57.7						

By studying the curve of excretion (Chart 1) for five- and ten-minute intervals it was found, however, that from 30 to 35 per cent. is excreted in the first ten minutes after appearance, this being half the total excretion for one hour. It at once becomes apparent, this being true, that observation for one-hour periods are subject to the same criticism that would apply to observation over four or five hours following subcutaneous injection or a study of total excretion. When intravenous administration is employed, observation for more than one-half hour should not be used, the amount of excretion for this time being almost equal to that for two hours following the subcutaneous injection. It has yet to be determined if the same reliance can be placed on the intravenous readings as can be placed on the subcutaneous, or especially on the lumbar method of administration, as well as what decrease in excretion occurs in disease following the intravenous administration.†

†Further investigation has shown that the intravenous method of administration is not as accurate as the intramuscular, especially where ureter collecters are employed. The normal variations in the functioning power for such short periods as fifteen minutes or one-half hour are too great.

The striking rapidity of elimination in the first few minutes following intravenous injection results, of course, from the concentration of the drug in the circulation, each cubic centimeter of blood going to the kidney-cells carrying more phthalein than by any other method of administration.

THE INFLUENCE OF VARIOUS DIURETICS ON THE EXCRETION OF SULPHONEPHTHALEIN

Because of the fact that many of the patients on whom the functional test is made are renal, cardiac, or cardiorenal cases, and therefore the subjects of [illegible], it becomes at once desirable to know what influence these various diuretics exert on the excretion of the drug in the urine; or, in other words, what changes in renal function, as indicated by the test, occur under [illegible] and to what extent these changes occur.

A study of the influence of diuretics is of value from another point of view, inasmuch as [illegible] considered with the [illegible], consequently allowing inferences to be drawn regarding the [illegible] of sulphonephthalein [illegible] these various diuretics exert on its excretion.

[illegible] have been used:

1. The effect of [illegible] administration on the output of [illegible]

The method [illegible] was as follows: [illegible] Into the other femoral a cannula [illegible] was inserted. [illegible] the neck of the bladder a [illegible] glass cannula with a capacity of only two or three [illegible] was tied into the opening in the bladder in such a way that the [illegible] flanged edge of the cannula came in apposition with the two ureteral openings, the apposition being such that in many instances on compression of the bladder-wall over the bell of the cannula, not a drop, or at most only one or two drops of urine, could be pressed from the distal end of the cannula. The abdominal wall was closed except at the exit of the bladder cannula and an incandescent electric light was placed just a few inches above the animal, the whole being covered with a large towel in order that the body temperature be maintained.

Under such conditions it was found that an excellent urinary secretion could be constantly obtained for long periods. Many of the animals having been given another small dose of chloretone together with hot milk by stomach-tube at the end of a day's experiment were found in such good condition the following morning that observations were continued throughout the second day.

From the burette the solution of sulphonephthalein was allowed to run into the femoral vein, 6 mg. of the drug being administered at the first injection. The phthalein was dissolved in either 0.8 per cent. salt or in Ringer's solution, in some instances 0.6 mg. to c.c., in others 2 mg. to [illegible]. The [illegible] was noted, this being usually from one and one-half to four minutes. Collections were then made usually for fifteen-minute periods, occasionally for twenty, and in one or two instances for one-half hour periods. At the end of each period the receptacle into which the urine drained was changed and sulphonephthalein was again allowed to run into the vein, a constant amount, usually 1.8 mg., for each period. Where the period was longer the amount of phthalein injected was of course greater, as for instance in Experiment 23, the amount of phthalein injected [illegible] 3 mg. in 1.5 c.c. Ringer's solution and the period of each collection one-half hour.

Collections were made for three or four such periods prior to administering any diuretic in order that an idea of the average excretion for each period could be had for comparison with the output under the influence of the diuretic. [illegible] the amount of phthalein remained approximately the same over periods of one to one and one-half hours, although the output of urine varied considerably.

The diuretic was now administered through the other femoral vein and its influence on the amount of urine, the amount of sulphonephthalein as estimated by the Dubosco colorimeter and on the reaction of the urine noted (sulphonephthalein serving as the indicator), observations in many instances covering a period of four to eight hours.

The accompanying charts represent the results obtained in some of these experiments. Each period lasted fifteen minutes, unless otherwise stated.

Caffein.—This exerts a stimulating influence on the secretory cells of the renal tubules and increases their secreting power; von Schroeder,[11] Anten,[12] Ach and Sullis[14] have demonstrated this unquestionably for the frog's kidney and the same presumably holds for mammals. Undoubtedly it is true that other factors, such as change of blood-pressure and increase in rate of flow through the kidney

11 v. Schroeder: Arch. f. exper. Path. u. Pharm., 1886, xxii, 39, and 1887 xxiv, 85.

12. Anten: Arch. internat. de pharmacodyn., 1901, viii, 453.

13. Ach: Arch. f. exper. Path. u. Pharm., 1900, xliv, 310.

14 Cullis: Jour. Physiol., 1906, xxxiv, 250.

Ach.[14] Fletcher, Henderson and Loewi[15]) are additional and important factors in the production of diuresis. The excretion of the solids under the influence of caffein (von Schroeder,[11] Loewi[16]) as well as the water output is augmented. Barcroft and Straub[17] show that there is a temporary increase in the metabolism followed by a decrease under the influence of this drug.

The effect of caffein on the excretion of sulphonephthalein is indicated in Experiment 14, Chart 3. The average output prior to the administration of caffein was 1.2 mg. for each fifteen minutes, and after the administration 1.5 mg. for the same length of time. Marked diuresis under the influence of caffein is therefore associated with an appreciable increase in the phthalein output.

Sodium Chlorid.—A rational explanation of saline diuresis is that advanced by Cushny.[18] The presence of hypertonic sodium chlorid in the blood disturbs the osmotic relationship and results in a great influx of water into the blood from

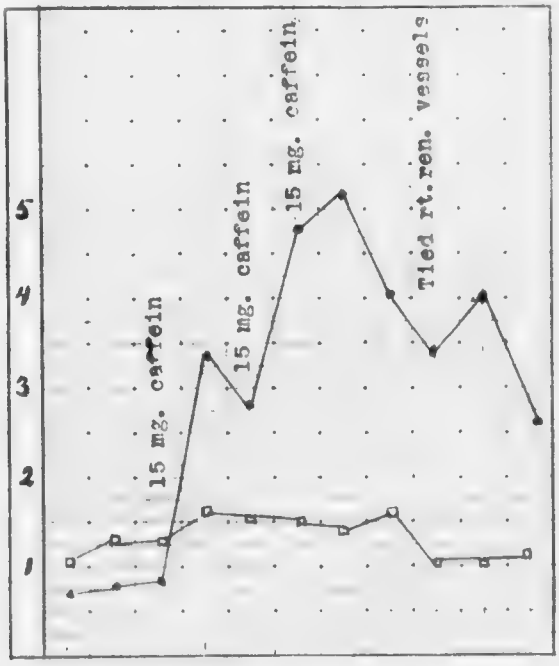

Chart 3.—Experiment 14. Cat. Chlorbutanol anesthesia. Influence of caffein on urine output, phthalein excretion and reaction of the urine. In this and the following charts the line with solid dots indicates c.c. of urine per period and the line with rectangles indicates mg. of phthalein excreted per period.

lymph spaces, hydremia resulting. The hydremia causes an increase in the capillary pressure in the glomeruli which in turn promotes the escape of fluid into the capsule. The resulting diluted urine rapidly flows through the tubules, short time only being presented for reabsorption, a marked increase in the

15. Loewi: Arch. f. exper. Path. u. Pharm., 1905, liii, 15.
16. Loewi: Arch. f. exper. Path. u. Pharm., 1902, xlviii, 411.
17. Barcroft and Straub: Jour. Physiol., 1911, xli, 145.
18. Cushny: Jour. Physiol., 1901, xxvii, 449, and 1902, xxviii, 431.

amount of urine secreted therefore results. This is a purely mechanical process and can be reproduced point for point in the dead animal (Sollmann).

Hypertonic sodium chlorid, even when the diuresis is enormous, causes no increase in output of sulphonephthalein; indeed the average output for fifteen-minute periods is slightly decreased from 1.25 mg. before to 1.15 mg. after the administration (Chart 4, Experiment 12). We know that the output of sodium chlorid under the conditions of this experiment is greatly increased and therefore conclude that the excretion of phthalein bears no relation to sodium chlorid excretion.

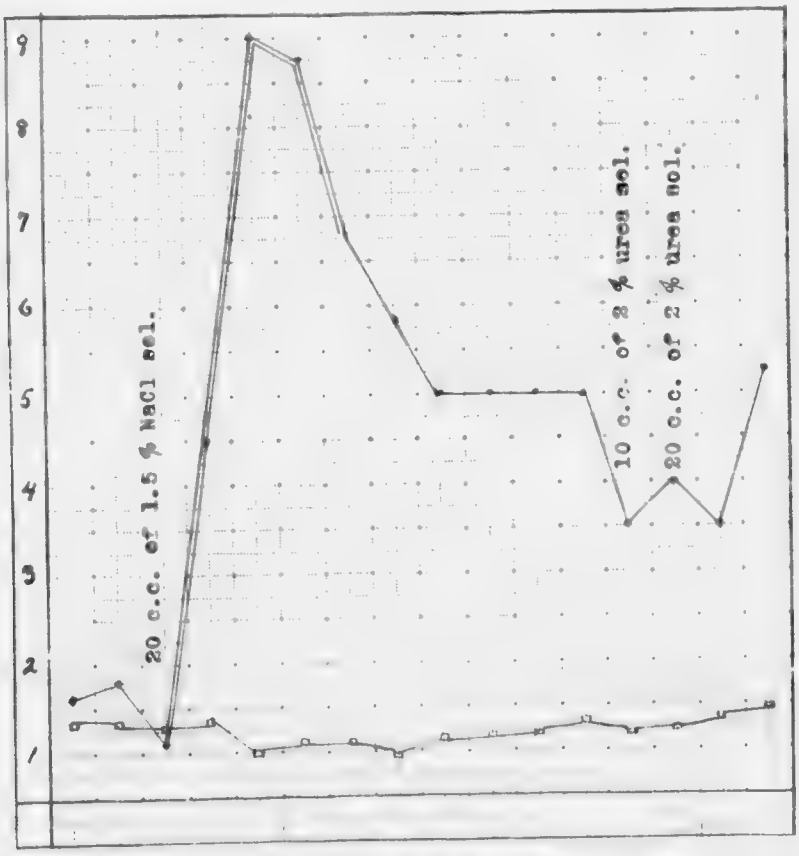

Chart 4.—Experiment 12. Cat. Chlorbutanol anesthesia. Effect of sodium chlorid and urea on urine output, phthalein excretion and reaction of the urine. In addition to the lines already explained the double line in this and following charts indicates distinct alkalinity of the urine

Urea.—Urea being a diffusible substance has been thought to produce diuresis in the same manner as sodium chlorid, that is by salt action. The work of Cullis, however, which we are able to confirm, shows that in the frog's kidney, when only the tubules are allowed to participate in the formation of urine, salines fail to produce diuresis, whereas urea elicits an abundant secretion. This certainly indicates that the action of urea differs somewhat from that of sodium

chlorid, in fact, it indicates that urea exerts a stimulating effect on the cells of the renal tubules just as caffein does. Furthermore, Barcroft and Straub have shown that during urea diuresis, more than the normal amount of work is per-

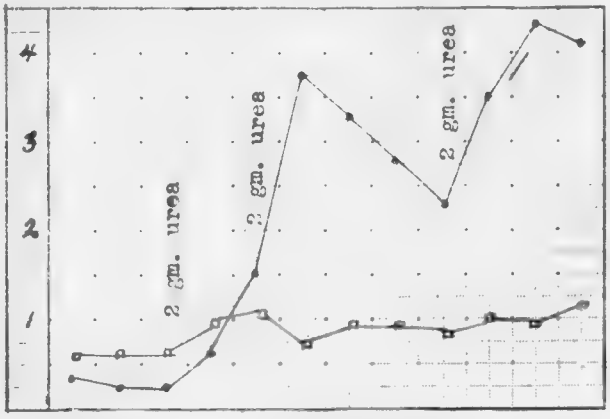

Chart 5.—Experiment 18. Cat. Chlorbutanol anesthesia. Effect of urea on urine output, phthalein excretion and reaction of the urine

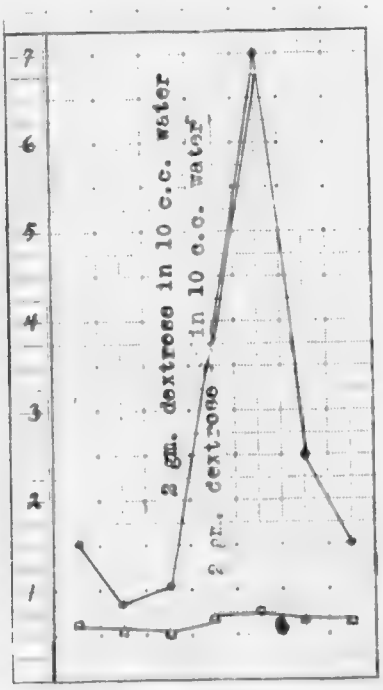

Chart 6.—Experiment 22. Cat. Chlorbutanol. Effect of dextrose on urine output, phthalein excretion and reaction of urine

formed by the cells of the tubules, no such increase being demonstrable during the course of a saline diuresis. The fact that urea increases the excretion of sulphonephthalein while sodium chlorid does not influence it at all, or decreases it, also suggests that a difference in the method of action exists. Whereas in our experiments sodium chlorid diuresis was accompanied by the early appearance of alkalinity which persisted for a long period, alkalinity was obtained only

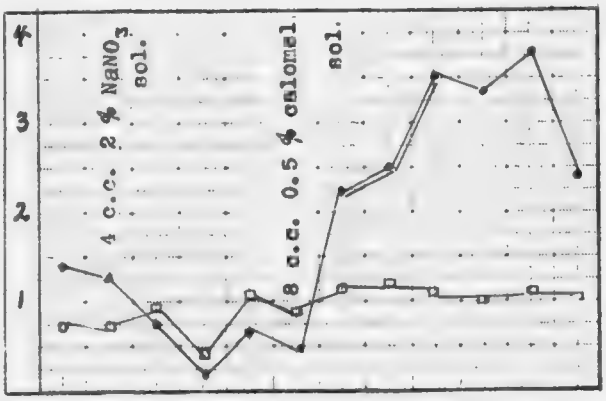

Chart 7.—Experiment 6. Cat. Chlorbutanol anesthesia. Effect of calomel on urine output, phthalein excretion and reaction of urine. Each period twenty minutes.

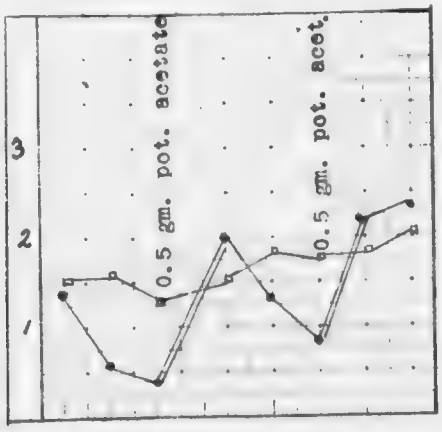

Chart 8.—Experiment 20. Cat. Chlorbutanol anesthesia. Effect of potassium acetate on urine output, phthalein excretion and reaction of urine.

with considerable difficulty during the urea diuresis, which is another point indicating difference in method of action. In one experiment (Chart 4) a slight decrease in the phthalein excretion under the influence of sodium chlorid and at the same time a slight increase under the influence of urea, while Chart 5, another experiment, shows a very definite increase in phthalein output under a urea diuresis. The difference in the alkalinity in the two experiments is striking.

Dextrose.—Dextrose resembles urea closely in its action. It is also capable of stimulating secretion by the tubules in frogs as was shown by Cullis.[14] Chart 6, Experiment 22, indicates that it also slightly increases the phthalein excretion.

Calomel.—Calomel is classified as an irritant diuretic raising the glomerular pressure by dilating the renal arterioles. It possibly stimulates also the vital secretory function of the renal cells. This latter is suggested by the decided increase of phthalein excretion in Chart 7, Experiment 6.

Potassium Acetate.—Although this is supposed to exert only a salt action, it will be seen from Chart 8, Experiment 20, that an increased phthalein output was elicited.

Digitalis.—Digitalis produces diuresis entirely through circulatory changes, i. e., increase in heart action and increased blood-supply regardless of the slight vasoconstriction which accompanies its use. The solids may not share at all in the diuresis. They remain the same or at most are but slightly increased. The phthalein output does not increase under the influence of digitalis, in some cases

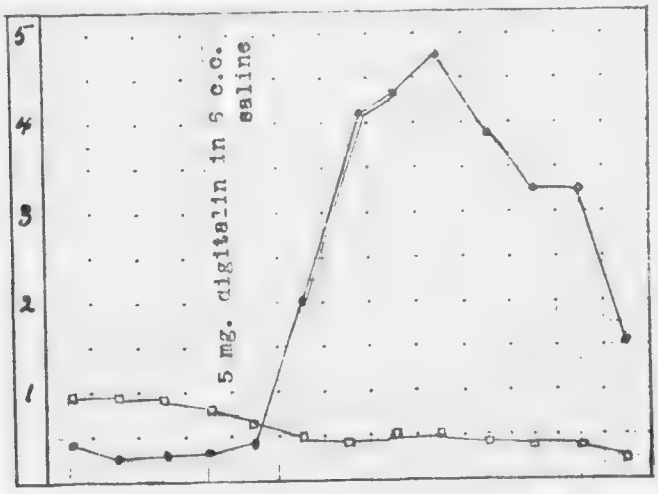

Chart 9.—Experiment 8. Cat. Chlorbutanol anesthesia. Effect of digitalis on urine output, phthalein excretion and reaction of the urine.

remaining the same. In one instance a decided decrease was encountered during the course of a marked diuresis (Chart 9, Experiment 6).

Phlorhizin.—According to Loewi[19] this is not a direct diuretic, the diuresis really resulting from a loss of reabsorption power in the tubules. Cullis,[14] on the other hand, shows that it has some direct stimulating effect on the tubules and also that by perfusing it through the frog's kidney a reducing body can be obtained. The work of Barcroft and Straub[17] also indicates that the secretion is an active process. As will be seen in Chart 10, Experiment 23, a slight increase from 1.75 to 1.93 mg. for one-half hour periods was obtained following its use.

Ringer's Solution.—Only a slight diuresis was obtained with Ringer's solution (see Chart 11, Experiment 21), and at the same time practically no effect on the phthalein output. Urea in this instance did not increase the phthalein output, this being the one instance in five experiments.

Potassium Nitrate.—Under the conditions of the experiment this salt produced diuresis while sodium nitrate failed on several occasions. The potassium ion must therefore play some rôle in the production of diuresis as well as the nitrate

19. Loewi: Arch. f. exper. Path. u. Pharm., 1903, l, 326.

ion. The salt as a diuretic falls into the same group as the sodium chlorid. Practically no influence is exerted on the phthalein excretion (Chart 12, Experiment 30), the average output before and after being 1.08 mg.

Under the conditions of our experiments it was found that those diuretics which are known to exert some stimulating influence on the activity of the secreting cells, or those diuretics in connection with which evidence is at hand indicating a stimulating action on the secreting cells

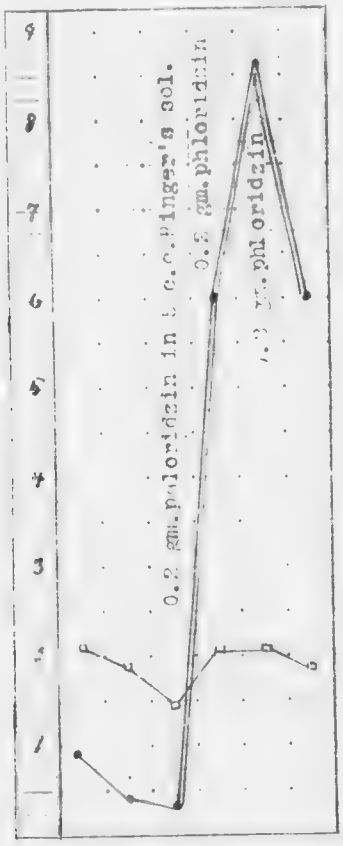

Chart 10.—Experiment 23. Cat. Effect of phlorhizin on urine output, phthalein excretion and reaction of the urine. Each period one-half hour.

(caffein, urea, dextrose, phlorhizin, calomel), slightly increase the phthalein output, whereas those diuretics which act entirely by changes in osmotic tension or by changes in blood-pressure, etc. (hypertonic sodium chlorid solution, potassium nitrate and digitalis), apparently have little or no effect on its excretion.

THE EFFECTS OF DIURETICS ON PHTHALEIN EXCRETION IN NORMAL INDIVIDUALS

The phthalein excretion following intramuscular (lumbar) injection was studied in a number of normal individuals who were then given by mouth various diuretics in the usual dosage for twenty-four hours previous to repeating the test. The collections were made for one hour following the time of appearance of the phthalein in the urine. The drugs employed were digitalis, calomel, diuretin, caffein, the ward

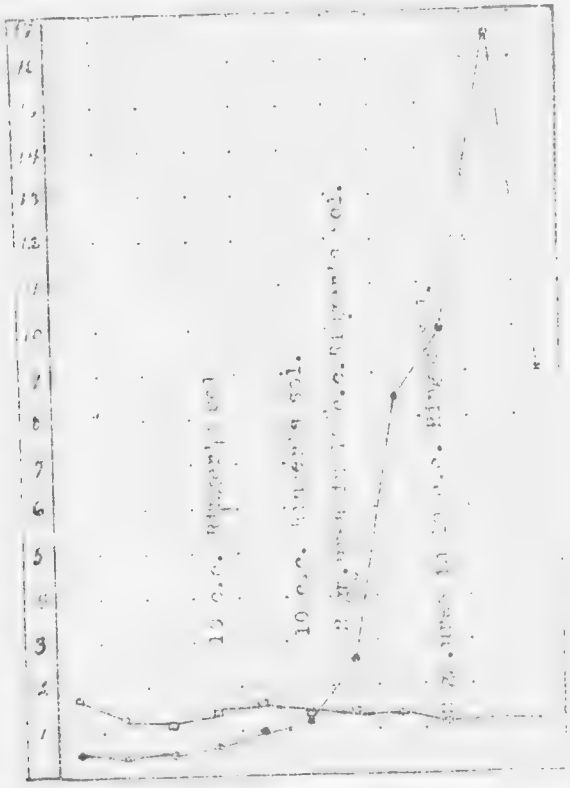

Chart II.—Experiment 21. C. C. Chloroform anesthesia. Effect of Ringer's solution and of urea on the urine output and phthalein excretion.

diuretic[20] usually employed at the Hospital, the Hospital, and Basham's mixture of iron.

[20] Ward diuretic:

Potassii Acetatis	5iv
Tr. Scillæ	5iij
Spts. Etheris Nitrosi	5iv
Aquæ q. s. ad	5iv
Misce. Sig. 5ii t. i. d.	

The results obtained may be seen in Table 5. No appreciable effect on phthalein excretion could be detected in any instance with the ordinary therapeutic dose. Relatively much larger doses were used in the animal experiments.

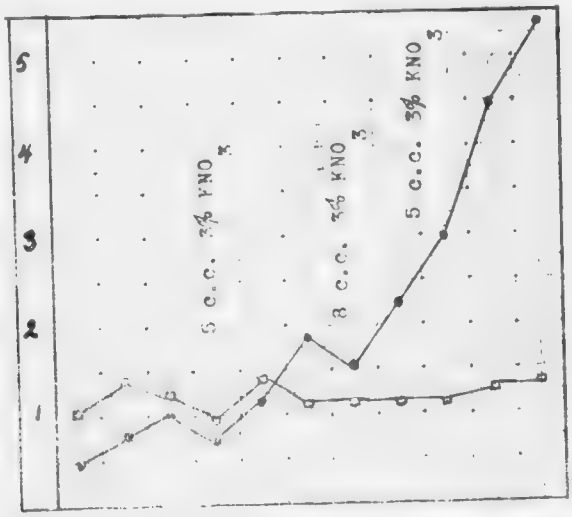

Chart 12.—Experiment 30, C. of C. Chloroform anesthesia. Effect of potassium nitrate on the urine output and phthalein excretion.

TABLE 5.—EFFECTS OF VARIOUS DIURETICS ON PHTHALEIN EXCRETION IN NORMAL INDIVIDUALS, FOLLOWING INTRAMUSCULAR (LUMBAR) INJECTIONS OF PHTHALEIN

Name	Normal Excretion Per cent.	Diuretic	Excretion After Diuretic Per cent
R.	62.5	Caffein gr. iii, t. i. d	62.5
M.	60.2	Diuretin gr. xv, q. 4 hr. for 24 hrs.	60.9
M.	60.2	Calomel gr. 1/10, q. ½ hr. up to 8 doses. Test 2 hrs. after last dose	60.2
S.	63.2	Diuretin gr. xv, q. 4 hr. for 24 hrs.	61.7
S.	63.2	Caffein gr. iii, t. i. d. for 24 hrs.	64.1
W.	48	Basham's mixture 3ii, q. 4 hr. for 24 hrs.	51.5
F.	56.4	Ditto	56.2
S.	46.7	Ward diuretic 3ii, q. 4 hr.	46.5
Y.*	60.9	Fr. digitalis m. xv, q. 3 hr. for 8 doses	60.2
	45.5		
	66.6		

*Subcutaneous injections.

THE INFLUENCE OF DIURESIS ON THE REACTION OF THE URINE

In 1872, Falck[21] called attention to the fact that the urine becomes alkaline following the administration of large amounts of salt solution

21. Falck: Virchow's Arch. f. path. Anat., 1872, lvi, 315.

by stomach or intravenously. Gruber[22] recorded similar observation in 1887. In his work on caffein, von Schroeder[11] encountered the same phenomenon invoked by this diuretic when the nerves to one kidney were destroyed. The urine from the side with diuresis was alkaline, that from the other side was still acid.

Rüdel,[23] in 1892, made a careful study of this subject working with numerous diuretics and found that alkalinity very commonly resulted. Katsuyama[24] studied particularly the influence of caffein, urea and diuretin in this respect. Under their influence the alkali, estimated as "alkaline chlorids," is greatly increased, sodium oxid is always increased, potassium oxid may or may not be increased, and these changes can occur under the influence of caffein even without marked diuresis. Urea [illegible] Diuretin increases markedly the alkalinity as "alkaline chlorids," sodium, potassium oxid, sodium oxid are all increased.

A change in reaction (alkaline urine) has been noted in many of our diuretic experiments. We have noted it after destroying the nerve connections of one kidney in two instances even when diuretics were not administered. In two other instances under similar conditions it failed to occur.

Under the conditions of our experiments, as set forth in the description of our work with diuretics on cats, alkalinity of the urine is indicated by the urine assuming a purplish-red color. The ease with which a change in reaction is provoked varies very considerably with the various diuretics.

III. SPECIFICITY DISPLAYED BY THE KIDNEY IN THE EXCRETION OF PHTHALEIN AND THE CONCENTRATION CAPACITY OF THE KIDNEY IN THIS REGARD

Six mg. of phthalein given subcutaneously to a patient weighing 60 kilograms yields a dilution in the ratio of 1 to 10,000,000. An infinitely dilute solution is presented to the kidney, which within one hour under normal conditions excretes 50 per cent. of these circulating molecules and passes them into the urine, sometimes as much as 5 mg. being excreted in 125 c.c. of the urine. A concentration of 1 to 4,000, or 2,500 times the concentration in the blood. When the amount of blood only is considered in the excretion of phthalein, the concentrating power still remains several hundred fold. Further 6 mg. given intravenously as much as 20 per cent can be excreted in five minutes in 2 or 3 c.c. of urine.

At the same time, in other instances, the same concentration is presented to the kidneys, to the pancreas, salivary glands, etc., and yet only

[22] Gruber: Inaug. Dissert. Leipzig, 1887, quoted from Rüdel.
[23] Rüdel: Arch. f. exper. Path. u. Pharm., 1892, xxx, 41.
[24] Katsuyama: Ztschr. f. physiol. Chem., 1899, xxvii, 587; 1901, xxxii, 239.

a small amount appears in the bile, while not a trace of it can be found in the pancreatic juice or saliva. The capacity of picking out the molecules of sulphonephthalein from infinitely dilute solution and passing them on into the secretion in comparatively concentrated solutions is therefore a function specific to the kidney.

MECHANISM OF EXCRETION OF SULPHONEPHTHALEIN

The ideal method of determining the mechanism whereby a dye substance is excreted is that which was adopted by Heidenhain,[25] in his work with indigo-carmin, i. e., to remove the kidney during the active secretion of the dye, fix the dye *in situ*, make sections and demonstrate the presence of granules of the dye in the cells actually engaged in excreting it. By this method he demonstrated that indigo-carmin was excreted by cells of the tubules.

This method cannot be utilized in connection with phenolsulphonephthalein, as all of the ordinary fixatives fail to fix this dye in the cells. Consequently it was found necessary to attempt to ascertain by other methods which part of the excreting mechanism is concerned in the excretion of this body.

EXCRETION BY THE FROG'S KIDNEY

The work of Nussbaum[26] indicating that the renal tubules in the frog's kidneys are supplied by the renal portal system, which is entirely separate and independent of the arterial supply to the glomeruli, although discredited by Adami,[27] was later shown by Nussbaum[28] and by Beddard[29] to be absolutely correct. The work of Cullis also affords striking confirmation.

Advantage was taken of this independence of circulation to the tubules in the frog's kidney, in an attempt to discover the method of excretion of sulphonephthalein.

Large male frogs, *Rana catesbiana*, weighing about 300 gm., were pithed, the abdomen opened by long incisions on each side of and parallel to the anterior abdominal vein. The left kidney was exposed and all the arterial connections severed by means of the Paquelin cautery, as suggested by Beddard. A cannula was then inserted into the anterior abdominal vein and a small glass catheter inserted into the left ureter. A protocol will indicate the course of the experiment and the results obtained.

Ringer's solution was perfused from a Mariotte flask through the renal portal system under a pressure of 35 cm. of water. Perfusion from

25. Heidenhain: Herman's Handbuch der Physiologie, v, 348.
26. Nussbaum: Pflüger's Arch., 1878, xvi, 139, and 1878, xvii, 580
27. Adami: Jour. Physiol., 1886, vi, 382
28. Nussbaum: Anat. Anzeiger, 1886, i, 67.
31. Beddard: Jour. Physiol., 1902, xxviii, 20

the renal portal vein for about fifteen seconds every three minutes was begun at 12:30 p. m. and continued until 2:25 p. m., no flow of urine resulting. At 2:25 the same solution, but now containing 1.5 per cent. urea and also phenolsulphonephthalein (60 mg. to 100 c.c.), was perfused. Diuresis became apparent at 2:40 p. m. At 3:50 p. m. the urine reached the distal end of the catheter and was found to contain considerable phthalein. At 4:10 p. m. a saturated aqueous solution of Prussian blue was injected, the kidney immediately removed and placed in absolute alcohol. Serial sections were later made but not a trace of blue could be found in any of the glomeruli. Identical results were obtained on adding caffein to Ringer's solution during the course of a purely venous perfusion.

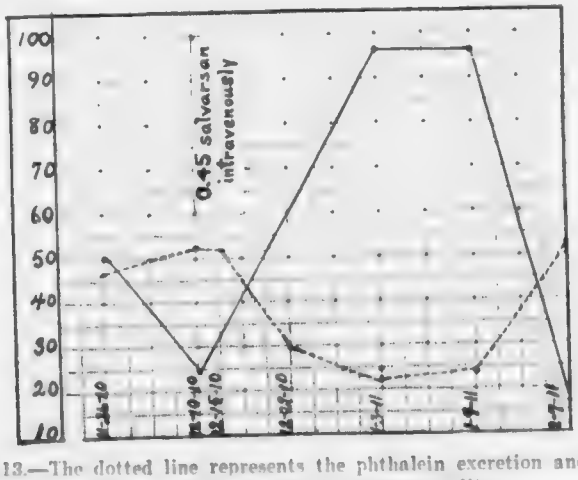

Chart 13.—The dotted line represents the phthalein excretion and the black line the amount of albumin in the urine in grams per liter.

This furnishes absolute proof that *phenolsulphonephthalein can be excreted by way of the cells of the tubules* in the frog and presumably the same holds true for mammals.

In another frog a purely arterial perfusion, by the method of Cullis, was made with hypertonic sodium chlorid solution. Here also the phthalein was excreted, but under these conditions both tubules and glomeruli participate.

THE INFLUENCE OF ANEMIA

Barcroft and Straub[17] have shown that after excluding the function of the renal tubules by profuse bleeding and the administration of large quantities of Ringer's solution, an isotonic urine, a pure glomerular filtrate can be obtained. The excretion of phthalein under such conditions was investigated. A protocol of an experiment in this connection follows (Table 6).

Cat. Weight, 2.8 kg. Injection, 0.7 gm. chloretone at 10 a. m. 12:26 injection of 6 mg. sulphonephthalein intravenously. At the end of each period 1.8 mg. of phthalein was given.

TABLE 6.—EXCRETION OF PHTHALEIN AFTER EXCLUSION OF FUNCTION OF RENAL TUBES BY BLEEDING

	Time	Quantity of Urine in c.c.	Mg. Phthalein Excreted
	....		
	....		
	12:43 p. m.	0.6	1.026
	12:58	0.6	0.951
	1:13	0.7	1.020
	1:28	0.6	0.789
	1:44	0.6	0.918
	1:58	0.8	0.714
1.	1:53—bled 33.5 c.c. and injected 40 c.c. Ringer's solution + 0.6 mg. phthalein extra.		
	2:15 p. m.	0.2	0.357
	2:28	1.2	1.128
	2:43	1.8	1.128
2.	2:42-2:47—bled 40 c.c. and injected 50 c.c. Ringer's.		
	2:58	0.9	0.618
	3:13	1.4	0.999
3.	3:08 to 3:12—bled 30 c.c. and injected 50 c.c. Ringer's + 0.6 mg. phthalein extra.		
	3:28	0.6	0.375
	3:43	0.4	0.300
	3:43 given 15 c.c. Ringer's solution.		
	3:58	0.4	0.234
	4:08 given 20 c.c. Ringer's solution.		
	4:14	0.4	
	4:29	0.8	0.267
4.	4:37—bled 35 c.c. and given 20 c.c. Ringer's solution.		
	4:47	0.9	0.270

The blood withdrawn was centrifuged and the amount of phthalein per cubic centimeter estimated, showing that the amount of drug in the blood increased considerably during the experiment, at first examination containing 0.0068 mg. per cubic centimeter, and in the last 0.0136 mg. per cubic centimeter.

In this experiment after profuse hemorrhage the excretion of phthalein decreased to approximately one-fourth of what it was normally, while at the same time the concentration of the drug in the blood was doubled: so that with severe anemia the excreting power of the kidney was decreased to one-eighth of normal.

Unless the bleeding be very profuse, however, little effect on the phthalein excretion will be noted, as can be seen from the preceding protocol (Table 8) and from the following protocol as well as from clinical evidence which will be presented later.

Cat.—Weight, 2.8 kg. Under chloretone anesthesia.

12:10 p. m.—5 c.c. 4 per cent. sodium chlorid solution.

12:26 p. m.—6 mg. phenolsulphonephthalein intravenously. Drug appeared in urine in two minutes and 18 per cent. was excreted in sixty-six minutes.

4:50 p. m.—50 c.c. of blood withdrawn and 60 c.c. of Locke's solution introduced in its place.

10:15 p. m.—10 c.c. of 4 per cent. sodium chlorid.
10:24 p. m.—6 mg. of sulphonephthalein administered. Drug appeared in two minutes and 27 per cent. was excreted in sixty-six minutes.

These results show that moderate degrees of anemia do not interfere with the excretion of phthalein, but that very severe degrees of anemia, which Straub and Barcroft have shown to result in the entire removal of the tubular function of the kidney, materially decrease the output of phthalein. This would indicate that the tubules are concerned in the excretion of phthalein but at the same time shows that the glomeruli also are capable of excreting some of this drug.

OTHER PHENOMENA BEARING ON THE METHOD OF EXCRETION OF SULPHONEPHTHALEIN

The fact that the output of phthalein bears no relation to the excretion of water and chlorids also suggests that the glomeruli play only a minor rôle in its excretion.

It is asserted by McKnider[32] that in experimentally induced acute tubular nephritis (produced by mercury bichlorid and by potassium chromate — see Schlayer and Hedinger[33]), there is a marked diminution in the excretion of phthalein. In the vascular type (produced by cantharides or arsenic) little or no decrease occurs at first but a decrease does occur later.[34] This also suggests that the glomeruli play a subsidiary rôle in the phthalein excretion.

The findings in our work with diuretics (discussed above) i. e., that those substances which probably act by stimulating into activity the renal cells, increase the phthalein output, while those diuretics which act only mechanically, as by changes in blood-pressure or in osmotic tension, do not influence the phthalein output, gives additional confirmation to the theory of activity on the part of the cells of the tubules in the excretion of phthalein.

THE STUDY OF NEPHRITIS

Heretofore functional tests have not been considered of any great value to the clinician in relation to nephritis. In fact hyperpermeability[35] to methylene-blue, indigocarmin and rosanilin has been shown to exist in acute and in chronic parenchymatous nephritis, while, on the other hand, decreased permeability with slow appearance and prolonged excretion has been demonstrated in the chronic interstitial variety.

32 McKnider: Personal communication.
33 Schlayer and Hedinger: Deutsch. Arch. f. klin. Med., 1907, xc, 1, and xci
34 The excretion of this drug in experimental nephritides is now under study
35 For literature concerning other functional tests see our original article. Jour. Pharm. and Exper. Therap., 1910, i, 577.

ACUTE NEPHRITIS

Thus far we have had opportunity to study only five cases of acute nephritis.

CASE 1.—The patient suffered from scarlatinal nephritis, had a severe angina and showed evidence of grave toxemia. It was impossible to determine whether the toxemia was due to the nephritis or to the angina. An injection of 6 mg. of the phthalein was followed by the appearance of the drug in the urine in twenty-three minutes. Forty-four per cent. of the drug was excreted in the first hour. This patient recovered and the nephritis completely cleared up in the course of a few weeks.

CASE 2.—A patient, with scarlatinal nephritis, was in bad clinical condition at the time of the first test. He had scanty urine of high specific gravity, smoky from blood and containing much albumin and many casts. The prognosis seemed bad.

The usual phthalein test was administered, the drug appearing in the urine in twenty-two minutes and only 4.8 per cent. being excreted in one hour. Three weeks later, the nephritis having almost disappeared and the clinical condition being greatly improved, as well as the condition of the urine, the test was repeated, showing the appearance of the drug in seven minutes and an excretion of 38.1 per cent. for one hour. Six weeks later the patient was entirely well and excreted 50 per cent. of a 30 mg. dose in the first hour.

CASE 3.—A boy of 7 years had a nephritis of obscure nature associated with purpura hemorrhagica and profuse hematuria. The time of appearance of the phthalein was not obtained, but the patient excreted 19.4 per cent. in the first hour and 19.1 per cent. in the second hour. Death occurred suddenly five days later from a suspected internal hemorrhage. No autopsy could be obtained.

CASE 4.—A boy, aged 8, was admitted with typical acute nephritis of a severe grade, the prognosis being considered unfavorable. The phthalein output on admission was 11 per cent. for two hours. Four days later the clinical condition was much better and the phthalein output had increased to 28.4 per cent. for two hours. Two weeks later the nephritis had practically cleared up and the phthalein excretion increased to 68.8 per cent. for two hours.

CASE 5.—The patient, J., aged 35, was well until a few weeks before admission (May, 1910), when he developed dyspnœa and marked edema. Marked anasarca, low urine output, high specific gravity, large amount of albumin and large number of casts were present. The heart was normal. There were no signs of uremia. The phthalein test, given subcutaneously, showed 20 per cent. excretion for two hours. The clinical condition became gradually worse. The patient died one week later without a second test.

The autopsy showed slight chronic diffuse nephritis with marked acute diffuse nephritis.

While no conclusions can be drawn from five cases, it is suggestive that in none of them was there increased permeability, but that on the contrary the permeability was markedly decreased when the condition was considered clinically grave. In some of the cases below, classed as chronic nephritis, an acute exacerbation was associated with the chronic nephritis at the time of the test. Here also the permeability was decreased but with the subsidence of the acute process the permeability increased.

It should be remembered, however, that when an acute process is present, variations in function may be very rapid and that a good clini-

nation on one day may be followed within a day or two by a marked decrease in function and *vice versa*. Consequently, in cases of this type the test should be repeated frequently.

CHRONIC PARENCHYMATOUS NEPHRITIS

In all, twenty-five cases belonging to the so-called type of parenchymatous nephritis have been studied. These cases represent different

TABLE 7.—PARENCHYMATOUS NEPHRITIS

Name.	Date.	Clinical Condition.	Time of Appearance (min.)	Am't of Urine (c.c.).	S. G.	Albumin.
1—L., aged 35...	12/6/09	Some edema and anemia	7	...	.....	++
2—R., aged 35...	12/10/09	Edema and mild anemia	30	10	1,032	++
	12/11/09	.....	20	13	.....	++
	12/13/09	.....	16	50	1,012	++
	12/24/10	Better clinically	25	23	1,036	++
	12/29/10	Better clinically	20	50	.....	++
3—R. L.	2/1/10	Symptoms two months; mild	..	114	1,017	++
4—W. L., aged 32.	1/28/10	Fair condition	9	412	1,010	++
5—M., aged 31...	3/5/10	Very mild symptoms; no edema; slight anemia.	8	312	1,005	++
6—G., aged 34...	3/15/10	Bad; mild uremia previous to admission.	22	125	1,013	++
7—P., aged 35....	2/1/10	Fair	6	...	.....	.....
8—J. J., aged 30.	4/4/10	Edema, anemia	10	305	1,007	+
9—P. S., aged 35. 75362	11/7/10	Edema, anemia	..	263	.....	+
10—M. A., aged 33 75555	11/6/10	Edema, dyspnea	..	134	1,011	++
	11/14/10	Apparently improved clinically	..	50	.....	++
11—B.	11/14/10	Slight edema at times; no other symptoms.	..	86	1,016	+
12—J. S., aged 57. 75581	11/21/10	Edema, dyspnea	..	80	1,009	++
	11/30/10	Uremic	..	135	1,012	++
13—K.	11/23/10	Edema; slight	..	116	1,030	++
14—C., aged 30....	11/26/10	Edema, anemia	..	168	1,030	++
	12/10/10	.....	..	77	1,030	++
	12/29/10	Given 0.45 salvarsan 12/15/10	..	...	.....	+++
	1/3/11	Clinical condition exceedingly grave	..	134	1,016	96 G. alb.
	1/9/11	No change	..	170	1,017	96 G. alb.
	1/17/11	Much better	..	226	1,018	+++
	2/7/11	Much better	..	166	1,024	++
15—S., aged 23...	1/25/11	No symptoms; nephritis detected accidentally.	..	112	1,022	+
	4/11/11	Intravenous injection	4	125	1,026	–
16—S. P., aged 29. 76996	2/10/11	Mild case	..	230	1,010	–
	4/20/11	Labor induced five days previous to test on account of threatened eclampsia; fair condition.	..	725	.....	Alb. 6 G to liter
17—Y., aged 48...	3/10/11	High blood tension, anemia, some edema.	..	374	1,008	–
18—Aged 28	7/7/10	Uremia; nausea and vomiting	..	100	...	++
19—D., aged 28...	3/20/11	Edema, dyspnea; clinically grave	..	150	1,026	++
	3/28/11	About same condition	..	70	1,016	++
20—E. W., aged 25.	4/21/11	No symptoms	7	73	1,014	–
	4/25/11	Lumbar injection	...	...	.....	–
21—P. S., aged 40. 77745	4/18/11	Edema; anuria for four days before admission.	..	65	1,019	– –
22—E. D., aged 10. 77423	3/28/11	Backache; no other symptoms	..	200	1,015	+
23—Aged 23	5/8/11	Acute nephritis one year; no edema; blood-pressure 90 mm. Hg	..	400	.....	5 G. to liter
24—Aged 30	5/6/11	Tuberculous arthritis; no clinical symptoms of nephritis	..	...	...	–

grades of severity and the duration of the disease varies from a few weeks to seven years. Details concerning these cases are seen in Table 7.

In five very mild cases of short duration showing only slight edema, with albumin and casts, but with a normal urinary output, the time of appearance of the drug and the amount excreted was normal. In one of these cases (No. 5, Table 7) the time of appearance was eight minutes and the output 52.5 per cent. for one hour. Another patient (No. 15)

TABLE 7.—PARENCHYMATOUS NEPHRITIS

Microscopical Findings	Per Cent. of Drug Excreted in		Remarks.
	One Hour.	Two Hours.	
Numerous casts.	14.2	....	Ureters catheterized and equal amounts from each side
Casts.	16.6	....	Impossible to increase urinary secretion by forcing water
Casts.	14.0	32.0	
Casts.	25.0	41.0	
Casts.	21.1	....	
Casts.	20.8	....	
Casts.	30.3	52.5	
Numerous casts.	11.9	26.6	
R. B. C.			
Casts.	52.5	....	
.....	4.4	10.0	Died of uremia two months later
.....	....	....	Given 30 mg., but output not estimated
Few casts.	20.2	42.2	
Casts	25.8	40.4	
Few casts.	2.9	6.2	Died 11/16/10. Autopsy: Severe amyloid nephritis, syphilitic; general amyloidosis
	....	Trace.	
Casts.	25.8	40.4	
Casts.	7.5	18.9	Recovered; reports herself feeling well at present except for edema (April 1, 1911).
Casts.	....	20.4	
Casts.	....	33.0	
Casts.	....	47.0	Left hospital in fair condition, but albumin (6 gm. per liter) and casts were still present
Casts.	33.3	51.6	
Casts	....	31.0	
Casts	....	22.0	
Casts		23.7	
Casts		43.1	
Casts.	....	52.7	
Few casts.	53.0	61.6	The excretion for first half hour after intravenous injection is below normal.
	Subcut.	....	
Few casts	54.4	*47.6	
Few casts.	....	51.0	
Many casts.	2.0	30.0	
Casts; few.	14.3	24.3	Symptoms for six years, only in winter
Casts.	No drug in 4 hrs.		Died two days later in uremia. No autopsy
Numerous casts.	6.9	....	Developed erysipelas and following this an empyema, which was drained. Died 4/10/11. Autopsy: Large white kidneys; subacute peritonitis
Numerous casts.	....	16.6	
Few casts.	36.7	....	Albumin and casts discovered accidentally.
Few casts.	Subcut inj.	....	
	51.0	....	
Numerous casts.	....	30.6	Voided freely after admission; edema disappeared in a few days. Discharged 4/18/11
Few casts.	....	66.6	Left hospital in a few days; felt perfectly well; albumin and casts still present
Many casts.	54.0	66.8	Clinically this case is considered to have a good prognosis
Some casts.	32.3	57.8	No symptoms of nephritis; albumin and casts discovered on routine examination

* Half-hour test

was a student who considered himself perfectly well but in whose urine albumin and casts were discovered by chance. On close inspection a slight edema about the eyes was detected. No other evidence or suggestion of the disease could be found. In this instance 53 per cent. for the first hour and 8.6 per cent. for the second hour was excreted following subcutaneous injection. After intravenous injection 46 per cent. was excreted for the first half hour (slightly decreased) and 17 per cent. for the following hour and a half. In three other cases a normal excretion was found but all three patients were free from symptoms, albumin and casts being the only indication of disease.

In cases of longer standing or cases in which the disease is of ordinary severity the time of appearance has always been delayed slightly (from ten to twenty-five minutes) and the amount excreted is definitely below normal.

In one patient (No. 2, Table 7) who has been under constant observation for more than a year the time of appearance (twenty minutes) and the amount excreted for one hour (20 per cent.) has remained practically unchanged. Clinically his condition is better than a year ago.

Another patient (No. 14, Table 7—see also Chart 13), age 30, admitted Nov. 25, 1910, with secondary lues and a definite parenchymatous nephritis of six months' duration showed an output of 47 per cent. for two hours at which time his urine contained 50 gm. albumin to the liter. December 10 his phthalein output was 51 per cent. and the albumin 25 gm. to the liter, while his general condition showed but little change. Because of the possibility of the nephritis being syphilitic in origin 0.45 gm. of salvarsan was given intravenously. December 26, his condition was definitely worse, urine decreased in amount and the albumin increased to 68 gm. to the liter, the phthalein output dropped to 31 per cent. January 3, his clinical condition was very grave, albumin 96 gm. to the liter and the phthalein excretion was 22.7 per cent. January 8, his condition was the same and the phthalein output unchanged. On January 17, however, his clinical condition was improved, albumin decreased in amount, and the phthalein output increased to 43 per cent. February 7, the patient was again in good clinical condition, the albumin only 6 gm. to the liter, while the output of phthalein increased to 52.7 per cent. The blood-pressure throughout ranged from 80 to 110 and no eye-changes were present. Although the phthalein output dropped *pari passu* with the exacerbation of the clinical manifestations, yet at no point did it reach a level which would indicate an immediate danger, whereas, clinically, death was considered imminent.

Another interesting case (No. 12, Table 7) is as follows:

Mrs. S., aged 57, admitted Nov. 16, 1910, with an acute exacerbation of a chronic nephritis. Symptoms of mild uremia were present and the urine contained 7 gm. albumin to the liter and many casts. The systolic blood-pressure was 190 mm. Hg. Her phthalein output was 19 per cent. for two hours. She gradually became more uremic and two weeks later was definitely comatose. At this time her phthalein output was 20 per cent., although her clinical condition was considered very grave. In a few days she regained consciousness and shortly afterward left the hospital. Ten weeks later the patient reported that with the exception of slight edema and dyspnea on exertion, all her symptoms had disappeared.

In the most severe grades of chronic parenchymatous nephritis or where the disease is of long standing and associated with secondary

sclerotic changes, the output is reduced very markedly, and in some instances no trace of the drug can be found in the urine. Here also, as in the interstitial type, the absolute failure of excretion, or the excretion of a mere trace, has been followed within a short time by death from renal failure. Some details regarding a few of these cases may be of interest.

Female, aged 28, admitted in August, 1910 (Case 18, Table 7). History of edema of face for over two years. Suffered some from headache. For a few months previous to admission had been unable to work on account of general weakness. On admission had nausea and occasional vomiting. Mentally clear. Marked anemia. Some edema of face. Urine contained large amount of albumin and numerous casts. Output of urine small. Phthalein test given and no trace of drug could be detected in the urine during the next three hours. She gradually became more uremic, the nausea and vomiting becoming rather continuous although mentally clear. Death occurred within four days. No autopsy was obtained.

Another case (No. 10, Table 7), one of syphilitic nephritis, was of rather peculiar interest. M. A., aged 23, admitted Oct. 24, 1910, exhibiting severe general anasarca and marked dyspnea. Symptoms had existed for one month. Pulse small and of low tension. Some anemia. No signs of uremia. Heart was normal. The urine had 6 gm. of albumin to the liter but no casts were found. Trace of sugar. Some days after admission hyaline casts were discovered. November 8, the albumin had increased to 30 gm. to the liter, although the dyspnea was better and the general edema somewhat decreased. The phthalein output was at this time only 6 per cent. for two hours. November 14, the general condition seemed about the same, but her phthalein output had decreased to a mere trace. The following day she became suddenly irrational and rapidly went into coma and died within twenty-four hours. Autopsy findings: Syphilitic hepatitis, general amyloidosis, especially of kidneys and spleen, thrombosis of right renal veins and veins of left side of pelvis.

Although the number of cases of chronic parenchymatous nephritis has not been very large, sufficient data have been collected to indicate that the test is of decided value in revealing the functional efficiency of the kidney in this condition. In the mild cases very little disturbance of function is indicated, and it may be impossible from the test alone to differentiate this condition from albuminuria unassociated with coarse renal lesions. When there is a marked decrease in the phthalein output marked renal changes are present, and when only excreted in traces, or not at all, a grave prognosis should be given even though no signs of uremia exist.

CHRONIC INTERSTITIAL NEPHRITIS

Twenty-three cases of the type clinically classed as chronic interstitial nephritis have been under observation (see Table 8). In many of these cases previous to the administration of the phthalein test no accurate idea of the degree of involvement of the renal function could be ascertained even after the most careful clinical study. The phthalein test has proved itself of immense value in revealing the degree of destruction of the renal substance, and has demonstrated itself to be of extreme importance from the standpoint of both diagnosis and prognosis.

Name.	Date.	Clinical Condition.	Time of Appearance (min.)	Amt. of Urine (c.c.).	S. G.	Albumin.
			32	...	.....	....
1—M.	12 6 09	.....				
2—F. S., aged 71.	2/1/10	Arteriosclerosis, mild cystitis; fair condition.	..	110	1,052	..
3—M., aged 48...	1 27 10	Arteriosclerosis, hypertrophy of heart, emphysema.	15	134	1,017	Alb. 1-3 G. to L.
			..	...	.....	
4—B., aged 55...	2/10/10	.....	15	45	1,020	Trace.
5—S., aged 56...	1/26/10	Arteriosclerosis	13	120	1,023	+
6—L. L., aged 52.	2/8/10	Good condition	12	62	1,024	Trace.
			..	...	1,023	+
7—McC., aged 65.	3 12 10	.....	..	560	1,006	Transient.
8—R., aged 51...	1 28 10	Typhoid; 2d relapse; 3d month of disease.	9	132	1,008	+
9—C., aged 39...	3 31 10	Good condition	8	470	1,006	+
10—H., aged 55...	1 13 10	Mild nephritis; good condition.....	..	132	.....	+
11—K., aged 43... 75401	11 7 10	Arteriosclerosis; high blood-pressure, 220 mm. Hg.	..	48	1,011	+
12—Mrs. W., aged 21. 75742	11 9, 10	Uremia; high grade choked disc; anemia severe.	..	102	1,015	Trace of albumin found a few times.
13—F. G., aged 71. 75741	11 9 10	Arteriosclerosis, osteo-arthritis; blood-pressure 220-225 mm. Hg.	..	...	.....	
			..	...	.....	
14—H., aged 65... 75949	11 21 10	Arteriosclerosis; blood-pressure 190-220 mm. Hg.	..	287	1,021	+
15—M. M., aged 37 75999	11 29 10	Nausea, headache, anemia; blood-pressure 215 mm. Hg.	..	130	1,008	+
	12 3 10	Condition worse	..	34	1,014	+
16—J. B. S., aged 63. 75948	12 3 10	Cerebral arteriosclerosis; attacks of unconsciousness; blood-pressure 180-200.	..	104	1,022	+
17—A. T., aged 69. 76109	12 13 10	Edema, dyspnea; blood-pressure 160-180..	..	48	1,020	+ +
18—H. G., aged 36 76496	1 7 11	Nausea and headache, hypothyroidism; blood-pressure 110-125.	..	127	1,012	Trace
	1 9 11	.....	..	110	1,009	Trace
	1 19 10	.....	..	70	1,010	....
	1 27 10	.....	..	170	1,007	....
19—Dr. H., aged 40	12 31 10	No symptoms	..	165	.....	+
20—C., aged 52...	1 26 10	No symptoms	..	210	.....	+
21—L. M. T., aged 60.	2 7 11	Nausea, headache; visual disturbances....	14	...	1,008	+
22—D. L. O., aged 47. 77449	3 24 11	Marked anemia, nausea; blood-pressure 130; no edema.	..	100	.....	Trace
23—W. T., aged 40 77268	3 24 11	Tuberculosis, osteomyelitis; persistent hiccough.	..	150	1,015	+
24—L. G., aged 12	3 28 11	Diagnosed on admission, diabetes insipidus; slight grade arteriosclerosis; blood pressure 80-90 mm. Hg.	..	340	1,005	0
	3 31 11	.....	..	420	1,005	0
25—S. B. G., aged 55	12 27 09	Slight headache, morning nausea; mentally clear; hypertrophy of prostate.	40	...	1,012	Trace
Surg. No. 25174	1 7 10	.....	30	...	.....	Trace
	1 10 10	Injection 30 mg. phthalein.....	23	...	.....	+
26—L., aged 50... 77885	4/25/11	Nausea, vomiting; blood-presure 190 mm. Hg.	..	120	1,020	Trace
27—D., aged 70...	4/11/11	Cerebral arteriosclerosis, myocarditis, emphysema; blood-pressure 160-215 mm. Hg	..	133	1,026	+ +
	5 7 11	Bad clinical condition	..	...	.....	+ +
28—F., aged 58...	4 24 11	Dyspnea, arteriosclerosis; blood-pressure 170-200.	..	360	1,010	+
29—Dr. S., aged 45	4 10 11	Marked cerebral arteriosclerosis; blood-pressure 200 mm. Hg.	..	52	1,026	+
30—P., aged 55 .. 77676	4 24 11	Arteriosclerosis and hypertension; blood-pressure 170; attacks of unconsciousness; drowsy and oncoming uremia suspected.	..	240	1,010	0 Trace on one occasion
			..	...	.....	
			..	...	.....	
31—W. B., aged 50 77260	3 30 11	Arteriosclerosis, cerebral arteriosclerosis, chronic nephritis; blood-pressure 185-240 mm. Hg	..	45	1,020	0
32—H., aged 56..	4 20 11	Marked eye-changes, partially blind; blood-pressure 190 mm. Hg; no edema; good physical condition	25	75	.....	+ +
33—P.	5/1 11	Arteriosclerosis, hypertension; good physical condition	..	...	.....	+
34—Dr. G. .	5 1 11	No symptoms except hyperacidity, gastric; trace of albumin and few casts for ten years.	..	...	.....	Trace

Microscopical Findings	Percentage of Drug Excreted in		Remarks.
	One Hour.	Two Hours.	
.....	....	....	Excreted about 1 per cent. for one hour; died in uremic convulsions two weeks later; no autopsy.
Hyal. and gran. casts.	34.5	48.3	
Numerous hyal. and gran. casts.	23.7	40.3	
No casts.	20.5	....	
Casts.	3.0	18.1	
Gran. and hyal. casts.	37.0	....	
Casts.	21.7	35.7	
Occas. casts.	22.7	45.5	
No casts.	31.0	....	
No casts.	36.3	....	
Few casts.	....	6.9	Died two months later; no autopsy; symptoms chronic uremia.
No casts.	0.0	0.0	Died 11/14/10. Autopsy: Small granular kidneys with superimposed acute hemorrhagic nephritis.
No casts.	5.0	15.0	Died 11/15/10, of broncho-pneumonia. Autopsy (3461): Atrophy of right kidney from old renal thrombosis; left, small, granular kidney.
Hyal. and gran. casts.	20.0	33.1	
Few casts.	....	11.6	Report 4/4/11: In bad condition; unable to get about; vomiting, headache, etc
Few casts.	....	3.8	
Few casts.	15.7	34.7	
Numerous casts.	....	20.8	
Few casts.	....	9.0	Discharged 10/7 11, feeling better; headaches and nausea some better.
Few casts.	....	6.9	
	....	4.6	
	....	8.0	
Casts.	20.0	49.0	
Casts.	18.5	38.5	
Numerous casts.	5.0	6.0	Died, uremia, 4/17/11; no autopsy.
No casts; few R. B. C.	0.0	0.0	Became drowsy, 3/27/11; died, uremia, 4/1/11; nephritis not suspected until test given.
Casts.	....	32.2	Died of tuberculous pneumonia; moderate grade of chronic nephritis.
No casts.	....	6.0	Trace of albumin found before admission; about 4/6/11, headache and trace of albumin and few casts in urine; died in uremia, 4/10/11 Autopsy: Extreme grade chronic interstitial nephritis.
No casts.	....	3.0	
0	....	Trace.	Died in coma, 1/19/10. Autopsy: Extreme grade interstitial nephritis; diffuse pyelonephritis.
0	....	Trace.	
	....	Trace.	
No casts.	0.0	0.0	Urea 15 per cent; catalase low; died in uremia, 4/27/11.
Casts.	....	15-25	Catalase low.
Casts.	....	12.5	
Casts.	....	38.1	
Numerous casts.	....	27.0	Craniotomy; following operation became drowsy; low urine output; died uremic convulsions one week later; probably acute exacerbation of nephritis following ether anesthesia
Few casts.	....	49.0	Some hematuria; no uremic symptoms developed.
Few casts.	....	17.0	Had symptoms on admission of slight cerebral hemorrhage
Casts.	2.0	8.0	Clinically considered very grave nephritis.
No casts.	....	50.0	
Occasional casts.	....	51.0	Blood-pressure not high; considered clinically to have only a slight grade of nephritis

In most of the cases of this series the time of appearance has been markedly delayed and the output of phthalein markedly decreased; where the output is lowest, the delay in appearance is most pronounced. The time of appearance, however, is not so important as the amount of excretion. Details of some of these cases demonstrate the accuracy of the phthalein test.

S. B. G. (No. 25, Table 8), aged 55, surgical No. 25,174. Admitted Dec. 21, 1909, complaining of difficult and frequent urination. These urinary symptoms were dependent on prostatic enlargement, the residual urine amounting to 440 c.c. Patient was apparently in good physical condition, well nourished but slightly anemic. Urine slightly cloudy, acid, specific gravity, 1010; no sugar, slight trace albumin and no casts. Urinary output 2,000 c.c. in twenty-four hours, urea ranging from 20 to 30 gm. for twenty-four hours. The phthalein test was given, a faint trace appearing in forty minutes and at no time was more than the merest trace detected. Repeated subsequent tests yielded always the same result. One week after admission he began to exhibit signs of uremia, which gradually increased until deep coma ending in death supervened. Autopsy: Both kidneys presented marked atrophy, neither organ weighing one-third of normal, a severe grade of interstitial nephritis being present.

This case is of particular interest because of the fact that the urinary output, the urea, the total solids and the total nitrogen were normal and casts were also absent.

The following is a history of a case in which the diagnosis was perfectly apparent clinically but in connection with which the test proved a striking confirmation as the phthalein failed to be eliminated.

Mrs. W. (No. 12, Table 8), aged 21, admitted November 7, with symptoms of uremia. Patient had had eclampsia in May, 1909, and had nearly recovered her former health. Suffered from frequent attacks of epistaxis, dyspnea, puffiness of eyelids and edema of ankles. On examination marked emaciation and pallor was noted. Red blood corpuscles 1,900,000, hemoglobin 22 per cent., high grade of chronic disk blood-pressure 230, temperature normal. Urine was somewhat decreased, specific gravity 1013 to 1019, albumin 1.9 gm. to the liter, no casts, acetone and diacetic acid positive at times.

The phthalein test was given the day after admission and showed entire absence of elimination during two hours.

Despite vigorous treatment, coma became deeper and death supervened five days later.

Autopsy (3460) showed an extreme grade of interstitial nephritis with a superimposed acute hemorrhagic nephritis.

In the following case the diagnosis was exceedingly obscure until the evidence brought forward by the test was added. Before the administration of the test, nephritis was only one of many possibilities entertained.

Mrs. O. (No. 22, Table 8), aged 47, admitted March 23, 1911. In October, 1910, noted fatigue and dyspnea on slight exertion, together with slight edema of lower extremities. In December nausea and vomiting developed and have been present almost constantly since. On examination patient was poorly nourished and showed marked anemia. Red blood-corpuscles 1,500,000; hemoglobin 15 per cent.; white blood-cells 6,000; slight increase in cardiac dulness, apex slightly

down and out, slight systolic murmur in pulmonary area; no edema of extremities. Urine: pale yellow; specific gravity 1011, albumin—a trace; *no casts on repeated examination.* Blood-pressure 135. Eye-grounds: negative. Although nauseated the patient was mentally bright and seemed in no imminent danger. The phthalein test showed no output in three hours. Two days later the patient became irrational, dying within forty-eight hours in uremic convulsions. No autopsy was obtained.

Chronic nephritis can exist over a long period without recognition and may even exist in the absence of albumin and casts in the urine. The following is another case illustrating the presence of nephritis in the absence of positive clinical proof, and also the value of the phthalein test in revealing its existence.

F. G. (No. 13, Table 8), aged 71, who had had six previous admissions (for malaria, febricula, acute rheumatic fever and arthritis deformans) during the last five years, was again admitted Nov. 7, 1910, for edema of feet and legs, vertigo and attacks of loss of consciousness. Numerous urinalyses during these admissions failed to demonstrate any anomaly except a trace of albumin at one single examination. An advanced arteriosclerosis and high blood-pressure were recorded on previous admissions. The chest was emphysematous, the heart sounds distant. Pulse 52, regular. Blood-pressure 220. Urine: pale, specific gravity 1012, acid, albumin occasional trace, no casts. Phthalein examination showed an output of only 5 per cent. for the first hour and 10 per cent. for the second, indicating a severe grade of nephritis. The next day definite signs of bronchopneumonia appeared, and the patient died five days later.

Autopsy (3461).—Atrophy of the right kidney as the result of an old thrombosis of right renal artery, with chronic diffuse nephritis on the left side, small granular kidney.

The following case is an example of the difficulty encountered at times in differentiating clinically various forms of toxemias from true nephritis with uremia.

S. E. (No. 17, Table 8), aged 55, admitted Jan. 3, 1911, in a drowsy toxic condition, had a history of chronic bronchitis of long standing associated with dyspnea. The present illness dated back two months, during which time the condition had become exaggerated. Temperature was from 99 to 100 F. Blood-pressure 160 mg. The physical examination of chest revealed a bronchitis and some myocarditis. The urine output was small, specific gravity 1030, acid, albumin 4 gm. to the liter, hyaline and granular casts. The physician in charge made a note saying "patient is certainly in uremia" and treatment for uremia was instituted. A phthalein test, however, showed an output of 52 per cent. for two hours which indicated a function not markedly impaired. Some days later the temperature rose to 103 F. and definite physical signs of a pneumonia became apparent. Patient recovered from pneumonia but exhibited myocardial symptoms. We have had another almost identical case of pneumonia in which the phthalein cleared up the diagnosis.

The following case shows even more strikingly the ability of the phthalein test to reveal the presence of nephritis in the absence of any definite clinical evidence, being a case in which nephritis was not suspected before the administration of the test.

TABLE 9.—PHTHALEIN OUTPUT IN

Name	Date	Clinical Condition	Time of Appearance (min.)	Amount of Urine (c.c.)	S. G.	Albumin.
1—Miss S., aged 57, 75881	11-29-10	Ac. exacerbation of a chr. nephritis; edema		80	1,009	++
	11-30-10	In uremia; drowsy............	..	135	1,012	++
2—M. A., aged 33, 75935	11-6-10	Syphilitic nephritis; dyspnea........	..	134	1,011	++
	11-14-10	Uremic	..	50	....	++
3—N. K., aged 43, 75401	11-7-10	Blood-pressure 220; had had suppression and slight drowsiness some days previous to test; no signs of uremia when test given	..	152	....	+
4—Miss W., aged 21, 75742	11-9-10	Nausea and vomiting; high grade choked disk; severe anemia	.	48	.....	+
5—M. M., aged 37, 75999	11-29-10	Edema, nervousness, headache; blood-pressure 215	..	130	1,008	++
	12-3-10	Nausea and vomiting; decreased urine output	.	34	1,014	++
6—H. G., aged 36, 76496	1-7-11	Hypothyroidism; nausea and headache; blood-pressure 110-125.	..	127	1,012	Trace.
	1-9-11	Condition unchanged	..	110	1,019	Trace
	1-19-11	Hydrargyrism acute	..	70	1,010	Trace.
	1-27-11	Better; no nausea or headache	.	170	1,007	Trace.
7—A. T., aged 43	12-13-10	General anasarca; myocarditis, arteriosclerosis, mitral insufficiency; blood-pressure 160-220	.	96	1,010	59 to L.
	12-19-10	Considered to have incipient uremia ..	.	96	1,012	+
8—G. G., aged 28	7-11-10	Nausea, vomiting; chr. parenchymatous nephritis	..	100	...	++
9—L. M. T., aged 60	2-7-11	Nausea, slight headache; chr. interstitial nephritis; visual disturbance	14	...	1,008	+
10—D. L. O., aged 17, 77449	2-7-11	Marked anasarca; nausea; blood-pressure 130; no edema; chronic interstitial nephritis		100	. ..	Trace.
11—S. B. G., aged 55, S. 25174	12-17-09	Slight headache; nausea in morning	40	.	1,010	Trace.
	1-7-10	Mentally clear; hypertrophy of prostate..	30	.	1,010	..
	1-14-10	[illegible]	23	[illegible]	[illegible]	.
12—M. ...	12-6-09	Chr. interstitial nephritis; symptoms of uremia appeared one week after test	..	...	.....	..
13—J. F., aged 37	1-3-11	Bilateral calculous pyonephrosis; nausea and vomiting		125	1,012	+
	1-7-11	Under hydrotherapy some improvement; nausea and vomiting better	.	125	1,022	+
	1-9-11	[illegible]		180	1,018	+
	1-11-11	[illegible] uremia ...		86	1,008	+
14—W. J., aged 71	2-11-10	Carcinoma of prostate, double pyelonephritis, slight nausea	60	230	1,012	+
	2-18-10	Has nausea and some vomiting ...	50	159	1,012	+
	3-8-10	Much better; no nausea or vomiting	23	135	1,014	+
	3-18-10	Feels well, general condition excellent...	16	252	1,014	.
15—A. W., aged 67, S. 24958	11-14-09	Hypertrophy of prostate, septic temperature	50	*	..	.
	11-24-09	Drowsy, temperature septic; uremic.....	38	[illegible]		.
	12-17-09	Better, but uremic; evening temp. 100 F.	18	154	1,005	+
	1-21-10	Good condition	15	390	1,006	+
16—W., aged 45		Pyonephritis of solitary kidney; vomiting and nausea severe		200		+
17—J., aged 35	4-10-11	In bad condition; no symptoms of uremia.	25	225	...	+
	5-7-10	Acute nephritis; edema; small urine output; not uremic	—	[illegible]	—	++
18—D. S., aged 45, 77672	4-11-11	Chr. nephritis; marked cerebral arteriosclerosis; blood-pressure 200 mm. Hg; no signs of uremia	—	...	....	
19— ...	4-15-11	Hypertrophy of prostate; moderate residual; history of uremic attack one year previously; given an intravenous injection of phthalein	7			
20—J. S. L., aged 50, 77883	4-27-11	Arteriosclerosis; chr. nephritis; blood-pressure 190		120	1,020	Trace
22— ...		Chr. interstitial nephritis; blood-pressure 180-200; hemorrhagic retinitis; general anasarca; moderate nausea and vomiting		250	1,010	++
24—L. G., aged 12, 77479	3-28-11	Diagnosed diabetes insipidus on admission; blood-pressure 85; no sign of uremia		340	1,005	0
	4-1-11	Nothing to suggest nephritis		430	1,005	0
25—F., aged 27 ...	12-10-10	Hypertrophy of prostate; pyuria........	[illegible]	[illegible]	[illegible]	+
	12-12-10	Has some fever; somewhat drowsy	23	...	[illegible]	

* No ... [illegible] ... Twelve hours after injection phthalein was still being excreted.
† Excret... [illegible] ... three hours and 40 per cent. for six hours. Urea, urinary output and total
seconds from ... [illegible]

TWENTY-FIVE CASES OF UREMIA

Microscopical Findings.	Percentage of Drug Excreted in		Remarks.
	One Hour.	Two Hours.	
Numerous casts.	7.5	18.9	Patient recovered in few days after last test.
Numerous casts.	....	20.4	Reports herself feeling well; edema still present.
Few casts.	2.0	6.2	Died 11/16/10; coma developed 11/15/10
Few casts.	....	Trace.	Autopsy: Severe amyloid nephritis
Few casts.	3.1	6.9	Died two weeks later; no autopsy.
No casts;	0.0	0.0	Died 11/14/10. Autopsy: Small granular kidneys with superimposed acute nephritis
Few casts.	....	11.6	Report 4/14/11, in bad condition; unable to get about; nausea, headache, etc.
Few casts.	....	3.8	
Few casts.	....	9.0	Discharged 2/7/11; headache and nausea better; died two months after leaving hospital with symptoms of uremia; nephritis was only regarded as a possibility in this case until phthalein test was performed
Few casts.	....	6.9	
Few casts.	....	4.6	
Few casts.	....	8.0	
0	....	20.0	Patient left hospital in fair condition; uremia did not develop
	..	29.4	
Numerous casts.	....	0.0	No drug in four hours; died two days later in uremia.
Numerous casts.	5.0	6.0	Died in uremia 4/17/11
No casts, few R. B. C.	0.0	0.0	Became drowsy 3/27/10; died in uremia 4/1/10.
0	....	Trace.	Died 1/19/11 in uremic coma. Autopsy: Extreme grade chronic interstitial nephritis and diffuse pyelonephritis
	....	Trace.	
	....	Trace.	
	Trace.	....	Died in uremic convulsions two months later; no autopsy
Cloudy from pus.	0.0	0.0	Double nephrotomy done rapidly under gas 1/11/11 in hope of giving some relief; died in uremia within twenty-four hours; kidneys were thin-walled pus sacs
Cloudy from pus.	....	Trace.	
Cloudy from pus.	....	5.5	
Cloudy from pus.	....	Faint trace	
Cloudy from pus.	0.0	13.8	For three hours total excretion 33 per cent
Cloudy from pus.	Trace.	14.8	For three hours total excretion 25.3 per cent
Cloudy from pus.	18.9	40.6	Perineal prostatotomy for removal of obstruction 3/21/10
.....	35.2	72.4	Still living 3/1/11
.....	....	....	
.....	....	....	
Cloudy from pus.	8.5	35.5	Perineal prostatotomy 12/22/09; good recovery; still living, in good condition, 5/1/11
Cloudy from pus.	23.6	57.0	
Cloudy from pus.	....	5.0	
Cloudy from pus.	6.0	13.0	
Numerous casts.	....	20.0	Condition became worse and died in coma one week later
Numerous casts.	....	27.0	Cranial exploration 4/14/11; following operation (ether anesthesia) was drowsy and had very low urinary output; died uremic convulsions one week later; probably acute exacerbation of his chronic nephritis.
Some casts.	¶	¶	Prostatectomy under long ether anesthesia 4/16/11; suppression of urine at once; died 4/20/11; no autopsy
Casts.	0.0	0.0	Urea 15‡; died in uremia two days later
Numerous casts.	1.0	4.0	Died in uremic convulsions two weeks later
0	....	6.0	Trace of albumin found once prior to admission; polyuria for two years; about 4/3/11 headaches appeared; 4/1/11, trace of albumin; died in uremia 4/9/11. Autopsy: Extreme grade of chronic interstitial nephritis; practically no renal cortex
0	....	3.0	
Pus.	18.5	43.5	Died about ten days after last test of uremia; no operation. Autopsy.
	8.0	13.0	Old chronic pyonephrosis of left kidney; right kidney hypertrophied, showing chr. diff. nephritis and marked diffuse acute pyelonephritis.

‡ Normal for [illegible] minutes
¶ First half hour 2% per cent. Normally this much excreted in less than ten minutes
Total excretion for one hour, 37 per cent

L. G. (No. 24, Table 8), aged 12, admitted March 27, 1911, as an interesting case of diabetes insipidus. The past history contained nothing of importance except that large quantities of urine had been voided for some time and he experienced marked thirst. He was well nourished, not anemic and apparently a normal-looking boy. His blood-pressure ranged around 100 mm. Hg. Some thickening of the radial arteries was noted; no definite eye-changes. The urine on admission was large in amount, from 2,000 to 2,500 c.c., clear, specific gravity 1005-1010. *No albumin, no casts.* At this time no suspicion of nephritis was entertained, although a trace of albumin had been noted once previous to admission. The phthalein test, performed March 28, showed an output of only 7 per cent. for two hours. Three days later only 3 per cent. was excreted. With the exception of the phthalein findings absolutely no evidences of nephritis were present at this date. A week later he developed headaches, and a trace of albumin in the urine appeared. He rapidly became uremic and died, April 9, 1911.

Autopsy: A most intense grade of chronic interstitial nephritis was present, with almost complete disappearance of the cortex. A slight grade of acute nephritis was superimposed.

UREMIA

In twenty-five cases under study uremia has been present (see Table 9). In sixteen of these the uremia was grave, the patients exhibiting nausea, vomiting, drowsiness or coma and in several instances convulsions. In the remaining nine, mild symptoms only were present and had persisted over long periods. Eleven of the sixteen patients with grave uremia died during the attack. *In all of these cases the phthalein elimination was zero or a faint trace only for two hours.*

Of the five patients recovering from their uremia, in two instances the output was 20 per cent., the uremia being the result of an acute exacerbation of a chronic nephritis. In two the output was 14 per cent.; in both of these the uremia was precipitated by a double pyelonephritis. The fifth case was an acute exacerbation in a case of chronic pyelonephritis in a man previously having had a nephrectomy. This last patient has greatly improved but at present has a two-hour excretion of 13 per cent.

In mild cases, exhibiting slight but persisting symptoms of uremia, the excretion respectively was as follows: 10 per cent. in one, 7 per cent. in three cases, a trace in one, 2 per cent. in the other for two hours. Four of the patients died within three months of the performance of the test. Those living are still exhibiting evidences of chronic uremia, four months having intervened in one instance.

In five patients who did not exhibit uremia at the time of the test but in whom the phthalein output was below 8 per cent. for two hours, one excreting 6 per cent. died within two months, one excreting 3 per cent. in one month, and the others are still living, one after four months, one after two months, and the other after three weeks, but all are at present exhibiting evidence of chronic uremia.

In two patients (Nos. 18 and 19, Table 9) not exhibiting uremia but with a markedly decreased phthalein output, operation with long ether anesthesia in each instance was followed by uremia and death.

CARDIAC AND CARDIORENAL CASES

An attempt has been made to differentiate by means of this test between those cardiac cases with broken compensation and passive congestion of the kidney, associated with the presence of albumin and casts in the urine and those cases in which cardiac insufficiency is associated with varying grades of true nephritis. In this connection thirty-three cases have been studied. There were eighteen cases in which the *purely clinical diagnosis* was that of uncomplicated cardiac disease, and fifteen cases of cardiac disease associated with nephritis. From a study of these cases there appears to be no doubt but that decrease in function accompanies marked passive congestion of the kidneys in the absence of any true nephritis. As the cardiac condition improves, however, the passive congestion becoming less marked and edema subsiding, the output of phthalein increases, and in one case rose from 16 per cent. to normal in the course of one week, the patient in the meantime losing seventy pounds in weight with the disappearance of a general anasarca.

The opportunity of comparing the result of the phthalein test with the findings at autopsy was afforded in the following case:

H. B. (No. 76710), aged 29, admitted Jan. 20, 1911, complaining of severe dyspnea and swelling of feet which had existed for two weeks only. Physical examination revealed markedly increased cardiac dulness, mitral and aortic insufficiency, dilatation of the heart, some ascites, bronchopneumonia, blood-pressure 190, moderate grade of secondary anemia. Urine: high-colored, specific gravity 1046, acid, albumin + + +, large number of hyaline and granular casts. Phthalein test showed an output of 26 per cent. for two hours. Patient died on the day following admission.

Autopsy: Chronic mitral and aortic endocarditis, chronic myocarditis, marked hypertrophy and dilatation of the heart, a moderate grade of chronic diffuse nephritis, with some superimposed acute nephritis. Death in this instance was in great part due to cardiac failure.

In those cases with broken compensation which presented a high phthalein excretion, in nearly every instance albumin and casts entirely disappeared with the improvement in the cardiac condition. An example of this class is the following case:

The patient, G. W., presented a severe grade of general anasarca with albumin and casts in the urine at the time of the test. He excreted 65.8 per cent. of phthalein in two hours. As the anasarca decreased, albumin and casts entirely disappeared, the kidneys showing no permanent injury from the break in compensation.

The presence of a general anasarca, particularly when edema exists at the point of injection, probably introduces some error from the standpoint of absorption. The extent of this error has yet to be determined. From a study of these cases we feel that the phthalein test will prove of value in determining what degree of renal insufficiency exists in this class of disease.

With improvement in the cardiac condition and the disappearance subsequently of edema, a continued low phthalein excretion will indicate with considerable certainty the presence of permanent organic changes in the kidneys. It should be noted, however, that a much larger series should be studied clinically and at autopsy before very definite conclusions can be drawn.

TABLE 10.—THE RELATION OF PHTHALEIN OUTPUT TO BLOOD-PRESSURE, TO CHANGES IN THE EYE GROUNDS AND TO THE BLOOD-PICTURE

Patient	Eye Grounds	Syst. Blood Pressure	Red Cells	Hb. Per cent.	Phthalein Output Per cent
Mrs. Y	[illegible]	220-280			32
Henry B	[illegible]	[illegible]	5,200,000	60	20
[illegible] C	Normal	260			55.5-1[illegible]
J.B	Normal	100-125	4,040,000	75	36
[illegible]	Normal	85-115	4,000,000	75	65.8
[illegible]	Normal		5,800,000	70	48
[illegible]	[illegible]	240	3,300,000	91	40
[illegible]		180-210			33.3
[illegible]		[illegible]-170	5,000,000	90	22.7
[illegible]		200	4,000,000	75	15
[illegible]		[illegible]	[illegible]	[illegible]	54.3
[illegible]	Normal	140-190	4,200,000	70	30
[illegible]	[illegible]	160-218	4,500,000	85	52
[illegible]	[illegible]	[illegible]-170	[illegible]	68	35.7
[illegible]	[illegible]	80-130	5,100,000	98	44.4
[illegible]		80-110	4,800,000	80	71.5
[illegible]	[illegible]	[illegible]-180	4,700,000	50	27.5 33.3
[illegible]		80-120	4,200,000	70	6.66
[illegible]	[illegible]	80-110	5,000,000	105	47.22 47.52
[illegible]		160-210	2,700,000	42	20
[illegible]		80-120	[illegible]	[illegible]	53.7
[illegible]	[illegible]	[illegible]	[illegible]	15	6
[illegible]	Normal	60-180	4,500,000	78	20.8
[illegible]		70-215	4,700,000	98	5
[illegible]		[illegible]	[illegible]	50	60.9
[illegible]	Neuroretinitis	[illegible]-140	4,200,000	62	3.8
[illegible]	Normal	[illegible]-120	[illegible]	75	1
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	Normal	[illegible]	[illegible]	94	60.1
[illegible]	Normal	[illegible]	[illegible]	80	26.3
[illegible]	Neuroretinitis	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	Neuroretinitis	[illegible]	[illegible]	95	65
[illegible]	[illegible]	[illegible]-[illegible]	1,900,000	22	0
[illegible]	Normal	[illegible]-140	4,500,000	71	20
[illegible]	Normal	[illegible]-180	5,000,000	74	[illegible]
[illegible]	Normal	[illegible]-235	4,500,000	80	15.5
[illegible]	Normal	[illegible]	[illegible]	[illegible]	50
[illegible]	Normal	[illegible]	[illegible]	70	0
[illegible]	[illegible]	[illegible]	[illegible]	75	11.3
[illegible]		[illegible]	[illegible]	[illegible]	40

MISCELLANEOUS CASES

A [illegible] miscellaneous medical diseases have been also examined from the standpoint of phthalein excretion, among the number being [illegible] cases of lobar pneumonia. Two of these cases exhibited ex[illegible]

dences of a mild nephritis during the attack, which was associated with a definite decrease in phthalein output. In both cases the urine was entirely normal one month later, as was also the phthalein output. In pneumonia the output is little if any decreased and bears no relation to the chlorid excretion.

Three cases of persistent albuminuria have shown a normal output. In no disease other than renal, so far studied, has marked reduction of the phthalein excretion been encountered.

THE RELATION OF PHTHALEIN OUTPUT TO BLOOD-PRESSURE, TO CHANGES IN THE EYE-GROUNDS, AND TO THE BLOOD-PICTURE

In the majority of cases of chronic nephritis in which the blood pressure has been high, the phthalein elimination has been markedly decreased, but no exact parallelism exists inasmuch as not a few instances have been encountered in which the systolic pressure has been over 200 mm. Hg and the phthalein output one-half of normal, while, on the other hand, there have been instances in which the blood-pressure has been normal while the phthalein output has been zero or nearly so, the patients shortly afterward dying in uremia. While a high blood-pressure when present is considered of diagnostic and prognostic value taken in conjunction with other clinical data, yet many patients died of renal insufficiency and exhibited a blood-pressure which was normal or practically so. Nor is the blood-pressure, even when high, increased in inverse proportion to the decrease in renal function.

While in some instances marked changes in the eye-grounds, choked disk, tortuous vessels, hemorrhages, etc., have been present coincident with a very low phthalein output, in many cases, even of the most advanced and even fatal nephritis, no changes whatever in the eye-grounds could be detected, the patient at the same time failing to eliminate the phthalein.

Moderate or rather severe grades of secondary anemia in the absence of disease of the kidneys can be present without any diminution in the phthalein elimination; for instance, two patients, one with 2,500,000 red cells and hemoglobin 30 per cent., the other with hemoglobin 30 per cent., eliminated 61 and 57 per cent., respectively, for two hours. A dog, with a red count of 7,290,000 and a phthalein output of 71.7 per cent. for one hour, was bled 120 c.c., resulting in red count of 5,400,000 and no change in phthalein excretion.

VALUE OF TEST FROM A SURGICAL STANDPOINT

Through the encouragement of Dr. Young we have been enabled to study the phthalein excretion in a large series of cases of urinary obstruction, in order to determine the value of the test in revealing the func-

renal capacity of the kidney in these cases. This is a consideration of grave importance in this connection, since the development of uremia or renal failure has been responsible for a great part of the mortality following surgical interference.

As a result of obstruction in the lower urinary tract, pathological changes may occur in the ureters and kidneys, dilatation of the ureters, varying grades of hydronephrosis, and, as a result of the continued high pressure, atrophy of the parenchyma of the kidney. Not infrequently infection occurs with the development of a pyelitis, a diffuse or localized pyelonephritis, or pyonephrosis. The occurrence of these complications is often difficult of recognition and is often overlooked, particularly in the absence of symptoms of renal inadequacy. A large proportion of these cases of urinary obstruction have cystitis associated with albuminuria. The presence of casts in the urine is no contra-indication to operation. The urinary output may be normal in many instances, also the urea and total solids, and yet the patient may be on the verge of renal failure and disastrous results may follow surgical interference.

The test has been used in at least 150 cases of urinary obstruction, mostly cases of prostatic hypertrophy. The technic involved in these cases necessitates the use of a catheter, otherwise it does not differ from that described above. For a detailed consideration of the value of this test in relation to obstruction in the lower urinary tract, see our previous publications on the phthalein test.[36]

In the majority of cases the test indicates more or less of renal impairment, and taken in conjunction with the clinical condition it is of more value than the study of urine output, total solids, total nitrogen and urea estimation combined.

A marked decrease in the amount excreted invariably means severe derangement of renal function, which may be of either a temporary or permanent character. Under such conditions one should proceed with extreme caution and no surgical intervention should be attempted without further study together with preliminary treatment. This preliminary treatment, as introduced some years ago into this clinic by Dr. Young, consists of drainage by means of a retention catheter or frequent catheterization, together with the administration of large quantities of water.

Under this regimen repeated functional tests will demonstrate eventually the nature of the derangement, for in true interstitial nephritis the output will continue low, whereas, if the derangement is purely functional or secondary to pyelonephritis, usually improvement will follow as a result of the treatment and will be indicated by a decrease in the time

36. See Reference 2, and also Ann. d. mal. d. Org. Gen.-Urin., February and March, 1911, and Tr. Am. Assn. Gen.-Urin. Surg., 1910

of appearance of the drug and simultaneously an increase in the amount eliminated.

The functional derangement due to infection in these cases is a much more dangerous condition than is the presence of even a fairly advanced condition of arteriosclerosis. The use of the test enables one to select a favorable time for operation. In cases exhibiting a continued suspiciously low output, the use of nitrous oxid gas or spinal anesthesia is suggested as preferable to ether in order to protect the kidneys. When only a trace of the drug continues to be excreted, operation should not be attempted at a favorable time or emergency, even though the patient presents no evidence of uremia.

In our original paper we stated that a dropping phthalein output was a contra-indication to operation except in cases of necessity. This decrease in function usually means some change in the renal condition and in most of our cases it has been caused by the development of a pyelonephritis or an exacerbation of an old process. It is obviously wise to wait until the kidneys have recovered from this acute stage before subjecting them to further injury through operation.

PRELIMINARY OBSTRUCTION

As regards the amount of excretion, below which one should not operate, we do not attempt to draw a definite line. The test simply indicates the renal function and it depends on the operator what risks he is willing to assume, the probabilities of fatality increasing as the phthalein output decreases. We do, however, recognize when we have low function which otherwise may be unrecognized and have found that preliminary treatment in most instances, whether it be by suprapubic, perineal or catheter drainage, allows a regeneration of function which will be indicated by the test and enables the patient later to undergo the graver operation of prostatectomy with less risk.

The test can be used to equal advantage preliminary to any surgical procedure where it is deemed important to know the true functional capacity of the kidneys.

TECHNIC OF THE PHTHALEIN TEST AS APPLIED TO ESTIMATION OF THE FUNCTION OF THE INDIVIDUAL KIDNEY

Functional tests have already demonstrated their great value in this connection. But they have at most been able to determine only the relative working capacity of each kidney and have shed very little light on the absolute functional capacity of each organ.

The phthalein test in association with ureteral catheterization has been used in seventy-five cases of unilateral or bilateral disease (Table 11), the technic being as follows. In most of these the subcutaneous administration was used. Recently, however, the intravenous method of adminis-

TABLE 11.—PHTHALEIN OUTPUT IN TWENTY-SIX

Number of Case and Name of Patient	Date	Diagnosis	Amt. of Drug Given in mg.	Time of Appearance (minutes)	Amt. Urine, Cc.	Reaction of Urine.†
43 Mrs. L.	[illegible]	Previous operation for right ureteral stricture	6	L.	330.0	+
				R.	215.0	+
44 E.	11 [illegible] 10	Tuberculosis of bladder and left kidney	6	L. 30	17.0	+
				R. 10	19.0	+
45 G. K.	[illegible] 10	Calculi right kidney	6	L.	170.0	+
				R.	190.0	+
46 P.	[illegible] 10	Tuberculosis of right kidney	6	L. 8	34.0	+
				R. 10	55.0	+
	12 [illegible] 10	Total function		....	70.0	..
47 B.	12 6 10	Tuberculosis of both kidneys	6	L. [illegible]	138.0	+
				R. 8	88.0	+
	12 [illegible] 10	Total function. Nephrectomy 12 15 10.			...	..
	12 [illegible] 10	Function of remaining kidney			...	..
	12 26 10	Function of remaining kidney			...	..
48 Mrs. Z.	[illegible] 7 10	[illegible] nephralgia, pelvic cap. 25 cc.	6	L.	150.0	+
				R.	150.0	+
49 L.	[illegible] 10	Left nephroptosis; pelvic dilatation 18 cc.	6	L. 8	53.0	+
				R. 8	53.0	+
50 F. M.	[illegible] 10	Calculi left kidney [illegible]	6	L. 16	17.5	+
				R. 11	24.5	+
51 K.	12 2[illegible] 10	[illegible] pyelonephritis, left	6	L. 1[illegible]	61.0	+
				R. 8	86.0	+
52 B.	12 27 10	Tuberculosis left kidney	6	L. [illegible]	50.0	+
				R. 8	59.0	+
	[illegible] 11	After nephrectomy function of remaining kidney	6	....	.....	..
53 De B.	12 [illegible] 10	Slight infection left kidney; previous nephrolithotomy	6	L. 8	66.0	+
				R. 7	109.0	+
54	1 6 11	Slight pelvic dilatation right side	6	L.	70.0	+
				R.	65.[illegible]	+
55 W.	1 7 11	Multiple abscesses left kidney; [illegible]	6	L.	125.[illegible]	..
				R.	210.0	.
56 B.	1 [illegible] 11	Tuberculous pyonephrosis right side	6	L.	240.0	.
				R.	?	.
	[illegible] 10 11	...				
57 O.	[illegible] 20 11	Hypernephroma right side	6	L. 10	200.0	+
				R. [illegible]	85.0	+
58 G.	1 26 11	Left renal calculus	6	L. 13	66.0	+
				R. 8	27.0	.
59 G.	1 [illegible] 11	Calculus lower end left ureter; marked hydronephrosis	6	L. 40	7.0	.
				R. 10	15.0	+
	1 [illegible] 11				.....	..
60 H.	[illegible] 4 11	Nephroptosis left side	6		115.0	+
					125.0	+
61 Mrs. A.	[illegible] 11	Probable double pyelonephritis, subacute	6	L.		+
				R.	.	+
62 A.	[illegible] 11	Enormous hydronephrosis of left kidney, 900 cc.		L. [illegible]	900.0	..
				R. 15	30.0	+
63 H.	[illegible] 18 11	Double pyelonephritis (No. 6 catheter used on left side; No. 8 on right)		L. 13	90.0	.
				R. 15	240.0	..
64 [illegible]	[illegible] 11	Slight infection of right kidney; possible stone		L. 7	11.0	.
				R. 8	11.0	
65 [illegible] B.	[illegible] 2[illegible] 11	Persistent fistula of left ureter following ureterolithotomy		L. 30	40.0	.
				R. 20	108.0	..
66 G.	[illegible] 10 11	Nephroptosis left side and hydronephrosis		L.	10.5	.
				R.	14.0	.
67 K. W.	[illegible] 5 11			L.	210.0	..
				R.	350.0	.
68 [illegible]	[illegible] 11	Multiple [illegible] calculi, right side		L. [illegible]	85.0	.
				R.	13.0	.
69 [illegible]	[illegible] 11	Slight pain in right renal region; few pus cells in bladder urine		L. 5	3.8	(15 min.)
				R. 9	3.8	(15 min.)
		(Second, 15 minutes)	...	L. 4.8	....	..
				R. 6.5	....	..

* Forty-two cases not shown in this table will be found in previous publication.
† Acid reaction indicated by plus; alkaline, by minus.

Chemical and Microscopical Findings	Percentage of Drug Excreted	Urea in Gm.	Remarks.
[illegible]	21.0	66.0	
[illegible]	17.0	21.5	
Pus and tubercle bacilli	2.0	10.0	Left collected transvesical; nephrectomy; badly diseased kidney; recovery.
Clear	34.0	32.0	
Cloudy; pus cells and cocci	15.0	57.0	Nephrotomy; lower one-third kidney filled with calculi, upper two-thirds normal; recovery.
Clear	20.0	68.0	
[illegible]	26.0	68.0	Nephrectomy 12/5/10; recovery; 12/7/10, 32 per cent. excreted one kidney one hour; 12/13/10, 28 per cent. excreted one kidney one hour; 12/20/10, 50 per cent. excreted one kidney one hour.
Cloudy, pale; pus cells few tubercle bacilli	17.5	44.0	
	45.0	....	
Slightly cloudy; pus cells; tubercle bacilli	26.0	96.0	Leakage of 27 c.c. with 6 per cent. urea and 3 per cent. phthalein, probably from left, as small catheter used on this side; nephrectomy, right side; recovery; kidney badly diseased.
Slightly cloudy; pus cells; tubercle bacilli	12.0	55.0	
	38.0	....	
	28.5	..	
	50.0	..	
[illegible]	18.0	45.0	Suspension; cure
[illegible]	19.2	22.5	
Clear; negative	15.2	61.0	Suspension; cure
Clear; negative	19.2	84.8	
R. B. corpuscles; no pus cells or bacteria.	9.0	31.5	Nephrolithotomy; cure.
Clear; no pus cells or bacteria	28.0	68.6	
Cloudy; pus; bacilli	10.0	36.6	Nephrectomy; recovery
[illegible]	22.0	86.0	
Cloudy; pus; bacilli	14.3	20.0	Nephrectomy; recovery; left collection transvesical.
	39.0	70.8	
[illegible]	43.0	....	
Hazy; cocci; no pus cells; trace albumin	20.0	42.9	No operation
Clear; no albumin	36.0	68.1	
[illegible]	26.0	....	Suspension
[illegible]	25.0	..	
[illegible]ly; pus	12.5	...	Nephrectomy; recovery
[illegible]	40.0	...	
[illegible]mun	16.0	...	Nephrectomy; recovery; left collected transvesical
[illegible]; pus	0.0	...	
[illegible]unction remaining kidney; [illegible]unction 1 hr., 10 min.	17.0	...	
Clear	44.0	100.0	Nephrectomy; death, fourth day, from hemorrhage; slight traces of right kidney only, almost entirely neoplastic.
Bloody	Trace.	25.5	
Red blood-corpuscles; few leukocytes	13.0	39.6	Nephrolithotomy; cure.
[illegible]	27.0	64.8	
[illegible]; few leukocytes	1.0	2.8	Removal of calculus; recovery.
Clear	21.0	21.0	
Total function without catheterization.	50.0	..	
Clear, no pus or bacteria.	15.0	..	No operation.
[illegible], no pus or bacteria.	18.0	..	
Clear; few pus cells	14.0	..	Nephrectomy, right side; congenital atrophy kidney with diffuse cortical infection; death sixth day, from pneumonia.
[illegible] few pus cells	1–2	..	Nephrectomy; large, thin-walled sac removed.
Blood (old)	0.0	..	
Clear	33.5	..	
Pus cells and cocci	5.2	90.0	Leakage 210 c.c. 1.5 per cent. urea and 10.2 per cent. phthalein leakage from left side probably.
[illegible] cells and cocci	9.0	32.0	
[illegible]dy; no pus, red blood corpuscles or bacteria	27.0	....	
Pus, bacilli and cocci	21.0	..	
[illegible]dy; pus cells	1.0	20.0	Nephrectomy; recovery; kidney showed severe old pyelonephritis
[illegible] pale	27.0	108.0	
[illegible]	Trace	13.0	
[illegible]	15.0	29.0	
[illegible]	15.8	100.6	Total function next day without catheters, 45 per cent.
[illegible]	12.8	100.3	
[illegible]	65.0	....	45 per cent. for one half hour
[illegible]	0.0	..	
[illegible]	23.0	6.7	Kidneys are apparently normal.
[illegible]	22.0	9.7	
[illegible]	11.0	8.6	
[illegible]	10.7	13.0	

ration has been employed, whereby the time necessitated for observation has been reduced to half an hour, collections being made at fifteen-minute intervals. Where it is desirable to determine whether the supposedly healthy kidney can assume sufficient function to permit of the removal of the other kidney, only a half-hour period of observation is necessary.

For the particulars concerning the technic of application of the test in association with ureteral catheterization, see our original publication.[3]

RESULTS OBTAINED WITH THE PHTHALEIN TEST IN UNILATERAL AND BILATERAL DISEASE OF THE KIDNEY

In normal cases the time of the appearance of the drug from the two sides has been almost always the same and in the majority of cases this has been five to ten minutes following subcutaneous and three to five minutes following intravenous injection. The time of appearance, of course, will vary somewhat with the rate of urinary secretion. Normally the amount excreted by each kidney will be practically the same.

The series of cases studied include tuberculous or pyogenic infection, unilateral or bilateral, calculi, hydronephrosis, hypernephromata, etc.[4]

When one kidney only is diseased, the time of the appearance of the drug is delayed on the diseased side and the amount excreted is not only relatively but absolutely decreased. The amount of delay in the time of appearance is comparatively of little value. Reliance is to be placed only on the quantity excreted during a period of one-quarter, one-half or one hour, depending on the method of administration.

Although in the majority of these cases of unilateral disease the combined output is equal to that of two normal kidneys, the greater part of the excretion is shown to be performed by the healthy kidney. In proportion to the decrease in function on the diseased side, approximately there is a proportionate increase in the function on the healthy side. In such cases following nephrectomy the remaining kidney eliminates, after the lapse of two or three weeks, an amount of drug which is normally excreted by two healthy kidneys. In all cases studied, the output from the remaining kidney has been greater than the combined output from the two kidneys prior to operation.

While the total urea from the combined urine is no true index of the functional activity of the kidneys, the comparative urea output from each kidney is of decided value. The same amount of urea is presented to each kidney for elimination, and therefore it is possible to estimate to some extent the proportionate amount of work which each kidney is performing. Barringer has pointed out that when the output from one kidney is four times as great as that from the other it is safe to remove

[3] The details concerning forty-two of these cases are considered in previous communications, Tr. Am. Assn. Gen. Urin. Surgeons, 1911, and Ann. d. Mal. d. Org. Gén.-Urin., February and March, 1911

the diseased kidney, provided that the urine from the opposite side gives no indication of disease. It is of most value when there is a marked disproportion from the two sides. This test, however, has its failings, as this proportion does not always exist. Again, the urea determination indicates only the relative amount of work that each kidney is performing, and as the exact amount of urea present in the blood is not known, the test shows only the relative activity of each kidney and not their absolute functional activity.

Again, it affords no indication as to whether the kidney is working at its ordinary capacity, or as to whether the reserve force is called on and the kidney is working at its maximum, and therefore unable to withstand any additional strain.

The inefficiency of these methods has necessitated the introduction of the more recent methods of estimating the functional ability.

A striking parallelism exists between the relative amounts of phthalein excreted and the relative urea output for any period, but the phthalein has an additional advantage inasmuch as it indicates not only the relative excreting capacity of the two kidneys, but furnishes an approximate idea of the absolute capacity of each kidney.

In all seventy-five cases of unilateral or bilateral renal disease have been studied in conjunction with ureteral catheterization, the series comprising cases of renal calculi, renal tuberculosis, non-tuberculous infection, hypernephromata, hydronephrosis and nephroptosis, ureteral calculi, ureteral strictures, hematuria, cases of polycystic kidney and a few miscellaneous cases.

In bilateral disease it has been found possible to determine the individual function (absolute or relative) of each kidney. It is in this class of cases particularly that the shortcomings of other functional tests have been most apparent, as one kidney may be doing twice or three times the amount of work of the opposite kidney and still be unable to assume the additional work of the other kidney. It may be doing the major part of the work at the expense of all or nearly all of its reserve power, but the phthalein test determines whether the kidney has a functional capacity which is normal, less than or greater than normal and to what degree. In two cases of double renal tuberculosis in which the amount of pus from each side was practically the same, the test permitted it to be determined that in each instance one kidney had a function greatly in excess of the other, indeed sufficient functional capacity to allow of successful nephrectomy, marked improvement in general condition occurring subsequently in each case.

The details of one of these cases are worthy of report:

B., aged 35, admitted Dec. 4, 1910, complaining of pyuria and some failure in general health.

Cystoscopic examination revealed a normal bladder. Separated urines yielded the following finding:

Left	Right
138 c.c.	88 c.c.
Cloudy	Cloudy
Pus cells	Pus cells
Tubercle bacilli	Tubercle bacilli
Albumin +	Albumin —
Urea 96 cg.	Urea 55 cg.
Phthalein appeared in 8 min.	Time of appearance 8 min.
26 per cent. for one hour	12 per cent phthalein

Leakage of 27 c.c. and 3 per cent. phthalein and 14 cg. of urea.

Although disease existed on both sides and from the character of the urine it was impossible to determine which side was more badly diseased, the phthalein indicated that the left kidney, although diseased, had the function of a normal kidney. The right kidney in this case was evidently the primary seat of disease. Nephrectomy of right kidney was successfully undertaken, being followed by a marked improvement in the patient's general condition.

The function of the left kidney gradually increased until the output at the end of three weeks was 50 per cent., equal to that of two normal kidneys. The kidney removed was badly diseased.

It seems probable that in this case the infection was limited to a local area and that the greater part of the kidney was healthy and subsequently was able to undergo compensatory hypertrophy.

In a case of bilateral pyonephrosis due to calculus, striking confirmation of the accuracy of the findings of the test was afforded by the following case:

L. E., aged 37, admitted Jan. 1, 1911, with vomiting and pain in epigastrium. Diagnosis: double renal calculi and pyonephrosis, uremia. In 1903 patient had right renal colic for first time, following which he passed two stones. Since then he had had two similar attacks on the left side. For last three months he has had frequent attacks of pain on the left side, dyspnea, vertigo and vomiting.

On examination patient was found markedly emaciated, hemoglobin 50 per cent.; red blood corpuscles 3,300,000; white blood cells 18,500. Kidneys not palpable; no tenderness. X-ray showed stones in both kidneys and in upper portion of left ureter. Urine: 1700 c.c. in twenty-four hours, specific gravity 1017, albumin + — and cloudy from pus.

Phthalein test January 2, no drug for two hours. Under forced water the urinary output increased and patient became less toxic, nausea and vomiting disappearing. Phthalein output was now 5 per cent. Two days later uremic symptoms reappeared and the phthalein output was again zero. A double nephrotomy under gas was rapidly done in the hope that some relief might be thus secured. Both kidneys were found to be merely thin-walled sacs filled with calculi and pus. Patient died in uremic convulsions in less than twenty-four hours.

The existence of an infantile kidney may be readily overlooked inasmuch as under normal conditions the urine from such a kidney may be absolutely normal so far as color, specific gravity and urea percentage are concerned. The literature abounds with numerous reports of death from renal failure following nephrectomy due to the inability to recognize

the presence of an infantile kidney. Recently, Kümmel[37] and McArthur[38] have each reported deaths following nephrectomy where an infantile kidney had been left to assume the work. In our series, two such kidneys, the seat of disease, have been removed, and in a third case with bladder tuberculosis and suspected renal tuberculosis without localizing symptoms on either side, an exploration of the left kidney revealed a healthy but infantile kidney. Exploration was necessary inasmuch as the bladder was markedly contracted and it was found impossible to catheterize the ureters. A similar condition was encountered in a cat utilized in our experimental work (described below).

The details of one of these cases is presented:

C., admitted March 19, 1910. Tuberculosis in an infantile kidney. The left ureter was catheterized but on account of ulceration of the right ureteral orifice it was found impossible to catheterize this ureter, the urine from this side therefore being collected transvesically. The separated urines were as follows:

Left	Right
30 c.c.	20 c.c.
Clear	Slightly cloudy
Normal	Some pus cells, no bacteria
Acid	Acid
Specific gravity 1020	Specific gravity 1016
Urea 28 per cent.	Urea 18 per cent.
Total urea 112 cg.	Total urea 34 cg.
Phthalein appeared 6 min.	Phthalein appeared 18 min.
Phthalein excreted 44.4 per cent.	1 per cent. excretion.

The right kidney was removed and was found to weigh 40 gm. The upper two-fifths were destroyed by tuberculosis.

When the disease is present in the large kidney nothing short of functional test will reveal the presence of the infantile kidney.

In certain cases, owing to malformation or strictures in the lower end of the ureters, and especially in bladder tuberculosis, it may be possible to catheterize one ureter only. When infection of the bladder exists, microscopical and chemical examination of the urine collected transvesically is obviously unreliable as an indication of a healthy or a diseased condition of the uncatheterized side. It is therefore necessary to resort to estimation of functional capacity in order to determine the presence or absence of disease on the side not catheterized.

In many instances of tuberculosis, as in the following case, it is the healthy kidney which can be catheterized and the absolute evidence of disease on the other side in the presence of an infected bladder must be ascertained, not by microscopical examination of the urine but by functional capacity.

Diagnosis: Tuberculosis of right kidney and stricture of lower end of ureter. Patient admitted with history of attacks of pain in the right kidney region and

37. Kümmel: Jour. Surg., Gyn. and Obst., April, 1911.
38. McArthur: Jour. Surg., Gyn. and Obst., April, 1911

an intermittent pyuria. A skiagram was negative: the bladder urine was clear but microscopically contained a few leukocytes, no organisms. Cystoscopy revealed a normal bladder. The left ureter was readily catheterized but an obstruction at the lower end of the right ureter obstructed the catheter on this side, necessitating transvesical collection. The separated urines were as follows:

Left	Right
45 c.c.	70 c.c.
Acid	Clear
Clear	Few leukocytes
Specific gravity 1024	No organisms
Urea 65 cg.	Acid
Phthalein appeared in 12 min.	Specific gravity 1004
32 per cent excreted	Urea 19 cg.
	Phthalein appeared in 20 min.
	5 per cent. excretion

On account of the low function and the presence of the ureteral stricture, a probable diagnosis of tuberculosis of the right kidney was made and a nephrectomy performed. On examination this kidney was found to be badly diseased, although the urine contained no pathological features.

Occasionally it is impossible to catheterize either ureter, particularly in marked vesical tuberculosis. Here by the aid of indigocarmin, noting the time of the appearance of the drug on each side and from the evidence obtained from cystoscopy and from localizing clinical symptoms, it will generally be possible to arrive at a probable diagnosis as to which kidney is involved. The total function as determined by means of phthalein will determine whether the disease is unilateral or bilateral. When one kidney is suspected and yet a good total renal function has been indicated, this side can be explored and if found to present evidence of marked disease can be removed with safety without exploration on the opposite side. Obviously excretion of a large amount of phthalein must have been performed by the opposite kidney. Such a case is here recorded:

The patient had marked vesical symptoms and pyuria with tubercle bacilli in the urine. On cystoscopic examination the whole trigone was badly inflamed and edematous. The right ureteral orifice was badly ulcerated and could not be catheterized. An attempt to catheterize the left side also failed on account of the edematous condition of the mucous membrane and the contracted condition of the bladder. This cystoscopic picture of the right ureteral orifice indicated probable disease of this kidney but disease of the opposite side, also, could not be excluded. A phthalein test for total function showed an excretion of 45 per cent. for one hour. A right-sided exploration revealed an advanced tuberculosis of this kidney and a nephrectomy was performed without exploration of the other side, which must have been responsible for the good renal function indicated by the test. The recovery was uneventful.

A patient, showing right-sided intermittent hematuria and chronic nephritis, admitted Sept. 19, 1910, had ureters catheterized and the separated urines yielded the following data:

Left	Right
13.5 c.c.	16 c.c.
Acid	Clear
Bloody	Acid
Urea 18 cg.	21 cg. urea
Phthalein 11 min.	Appeared 11 min
11 per cent. excreted	11 per cent. excreted

The following day total function without catheterization was studied, output being 22 per cent. The equal and decreased function as indicated by the phthalein showed a bilateral renal disease due to chronic nephritis. A few casts were found in the urine.

The value of the phthalein output over that of urea is strikingly demonstrated in the case just cited, elimination being practically equal for the two sides, but no indication was afforded of the reduced total renal function.

In two out of three cases with hypernephroma a decrease in function was indicated. In the third case no difference in function for the two sides was indicated. The phthalein, the urea, specific gravity and quantity of urine collected from each side were identical and normal. On account of pain due to a slight hydronephrosis, the kidney was explored and the tumor discovered. The hypernephroma had not invaded the kidney but was simply attached to its upper pole, in all likelihood not interfering at all with renal function.

The test has been used by us simultaneously with cystoscopy, phloridzin, indigocarmin and the polyuria test of Albarran. No particular advantage was added by combining with one or all. Indigocarmin and phenolsulphonephthalein can be combined as follows: Following the appearance of phthalein after injection, 5 c.c. of 4 per cent. indigocarmin suspension is injected into the gluteal muscles and the time of appearance in the acid urine noted. While the amount of phthalein excreted can be estimated with a fair degree of accuracy in the presence of indigocarmin by rendering the urine alkaline and boiling, on the other hand the amount of indigocarmin excreted can be estimated after acidifying with hydrochloric acid or sulphuric acid at the best only roughly, and occasionally not at all. When the two tests are used simultaneously the whole test is complicated with the introduction of no advantages and some disadvantages.

In the following case, with a painful kidney, with old healed pyelonephritis various functional tests were combined, urea, phloridzin, cryoscopy and polyuria.

Left	Right
325 c.c.	80 c.c.
Specific gravity 1010	Specific gravity 1009
Urea 40.6 cg.	Urea 8 cg.
Phthalein appeared 7 min.	Phthalein appeared 8 min.
Excretion 25 per cent for 1 hr.	Excretion 8.8 per cent.

Phloridzin test, injected 5 mg. Sugar appeared in 15 min. Trace in 35 minutes: 1.95 gm. in 1 hour.

Cryoscopy, urine for first 20 minutes. 44 c.c.Δ —0.09 22Δ—0.15.

Polyuria test:

Left	Right
44 c.c.	22 c.c.
120 c.c.	22 c.c.
158 c.c.	41 c.c.

Urine collected in 20 minute periods.

INHIBITION OF FUNCTION AS THE RESULT OF URETERAL CATHETERIZATION

As pointed out by Kapsammer,[39] a change in function of the kidney sometimes results from the introduction of the ureteral catheters and may occasionally seriously interfere with the value of quantitative determinations of the renal function. Following catheterization anuria is most frequent but sometimes polyuria occurs and even in the presence of polyuria inhibition of secreting function, urea, etc., may be present. In our series a moderate grade of inhibition has been noted in six cases out of seventy. This inhibitory influence of the catheters can be readily detected by determining the total function without the use of catheters which should always be done as a control. In no instance in our series was the inhibition of such a grade as to interfere seriously with the value of the test. This inhibition of function from ureter catheters has also been noted by Keyes, Jr., and A. R. Stevens.[40] The most serious disturbance in our experience occurs shortly after the introduction of the catheters and it is wise to wait until the catheters are working freely and smoothly before giving the phthalein injection. If this technic is followed, inhibition will probably not play an important rôle in the great majority of cases.

RENAL FUNCTION BEFORE AND AFTER NEPHRECTOMY

This problem has been investigated from the experimental and from the clinical side. The cats employed in the diuretic work referred to above were utilized also for the study of this problem. During the course of active secretion one kidney was suddenly tied off, the quantitative secretion of urine and phthalein being subsequently studied and compared with the excretion prior to this nephrectomy, the conditions of the experiment of course being kept absolutely the same after the removal of the one kidney. In the majority of instances a slight fall both in the quantity of urine and in the phthalein excretion occurred immediately after tying off the one kidney. Occasionally the phthalein remained the same for one-quarter or one-half hour and then gradually fell, and in one instance the urinary flow was increased while the phthalein output remained practically the same.

One case is of particular interest inasmuch as the removal of one kidney greatly reduced the urinary flow and at the same time reduced the phthalein output to one-fifth of its former level. This finding was unique. In this case, however, it was found that the remaining kidney was congenitally atrophic or infantile in character and weighed only 6.4 gm., while the kidney which had been removed weighed 26.4 gm. This is a striking example of the value of the test in detecting the true functional capacity of a kidney.

39. Kapsammer: See original paper, Ref. 2
40. Keyes: Personal communication

The function of the two kidneys on the day of the operation has been estimated and compared with the function of the remaining kidney as it is on the day following operation. Chart 14 shows the curve of excretion prior to and the day following nephrectomy in a dog, the estimations being made at five-minute intervals after the appearance of the drug in the urine following an intravenous injection of 6 mg. of phthalein. Although the rate of excretion is somewhat slower, no great decrease in function is indicated at the end of a half-hour's observation.

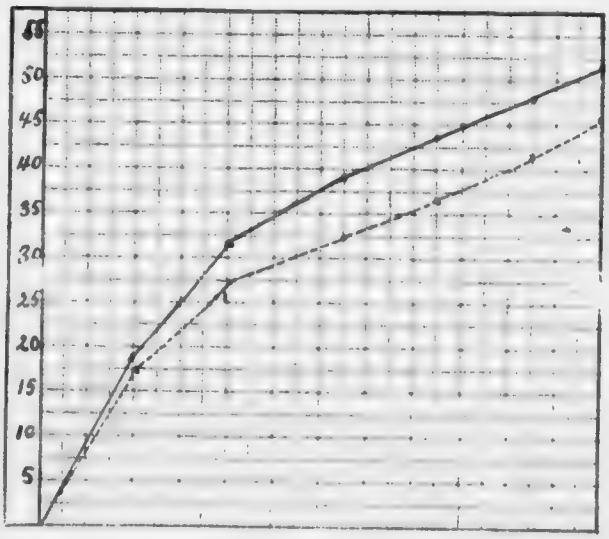

Chart 14.—The upper line represents the phthalein excretion for one-half hour following intravenous injection, the estimations being made at five minute intervals. The lower line represents the excretion in the same dog for one kidney within twenty-four hours after nephrectomy.

In those cases in which the function of the remaining healthy kidney was estimated after an interval of three weeks to one month following nephrectomy, the function was invariably found not merely to equal the combined function of the diseased and healthy kidney prior to operation, but to be definitely greater. In a few cases in which the function was estimated at an interval of a few days to a week following nephrectomy, the function corresponds very closely to that which existed in that kidney previous to operation, but at the end of a period of three weeks or a month the function was always equal to that of two normal kidneys.

In one case of double renal tuberculosis in which the function of the kidney left behind was 26 per cent. for one hour prior to operation, it increased until at the end of one month a phthalein excretion of 50 per cent. for one hour was attained, which was considerably greater than the combined function of the two kidneys prior to operation. In this instance

TABLE 12.—AUTOPSY

Name.	Date.	Clinical Diagnosis.	Microscopical Findings
1—R., aged 39... 77401	3/28/11	Acute endocardiitis, mitral insufficiency dyspnea; no edema at time of test; developed later acute nephritis.	Alb. +; few casts.
2—L., aged 46.... 77543	3/28/11	Arteriosclerosis, aortic insufficiency, acute endocarditis, dyspnea, some edema of legs.	.....
3—G., aged 71... 75741	11/9/10	Arteriosclerosis, bronchopneumonia, hypertrophic arthritis deformans; blood-pressure 220-225.	Trace alb. and occas. cast.
4—T., aged 35... 77268	3/24/11	Chronic osteomyelitis; developed a tuberculous pneumonia.	Alb. +, and casts.
5—McC., about 60	3/31/10	Hypertrophy prostate, small residual.....	28 c.c. of urine excreted in two hours.
6—M. A., aged 33 75555	11/6/10	Syphilitic nephritis, edema.....	Alb. ++; few casts, clear.
	11/14/10	Uremic	Alb. ++; casts.
7—Mrs. W., aged 21, 75742	11/9/10	Nausea and vomiting; high-grade choked disk; severe anemia; definite uremia.	Alb. +; no casts.
8—T. E., aged 37.	1/3/11	Bilateral calculous pyonephritis; uremia.....	Alb. +; cloudy from pus.
	1/7/11	Some improvement, not so much nausea.....	Alb. +; cloudy from pus.
	1/9/11	Improving	Alb. +; cloudy from pus.
	1/11/11	Again severely uremic.....	.....
9—L., aged 76... Surg. No. 25319	1/22/10	Hypertrophy prostate, large residual, myocarditis, some dyspnea.	Alb. + and casts; clear.
	1/29/10	Condition seems better; has had retention catheter.	Alb. + and casts; cloudy.
	2/4/10	Condition same	Urine pale; cloudy from pus.
10—G., aged 55... Surg. No. 25174	12/22/09	Hypertrophy of prostate, large residual, some anemia, slight nausea and vomiting.	Trace alb., slightly cloudy from pus.
	1/7/10	Retention catheter; condition same; up and about ward; urine output, 2-3 liters; urea, 25-30 gm.	Urine more cloudy.
	1/10/10	More nausea and vomiting; injec. 30 mg.....	Cloudy.
11—H. T., aged 20, 76691	1/20/11	Acute pneumonia; died 1/27/11, of abscess and gangrene of lung.	.....
12—G., aged 12... 77459	3/28/11	Diabetes insipidus clinical diagnosis; no signs of nephritis.	Negative.
	3/31/11	Same condition	No alb. or casts.
13—D., aged 44. 77782	4/19/11	Arteriosclerosis, chr. nephritis, myocarditis, pericarditis, edema, dyspnea, Von Graefe; blood-pressure 110.	Alb. ++; few casts.
14—B., aged 29... 76710	1/20/11	Chr. nephritis, aortic and mitral insufficiency, general anasarca, dyspnea; in bad condition but not uremic; blood-pressure 190.	Alb. +++ and showers of casts.
15—O., aged 63...	1/20/11	Hypernephroma of right kidney.....	200 c.c. from right.
16—T., aged 60...	7/?/10	Complete retention, due to contraction of vesical neck; chr. abscess space of Retzius; bad clinical condition; bad cystitis.	Cloudy; pus; small amount alb.
17—P., aged 77...	12/10/10	Hypertrophy of prostate; pyuria.....	Pus and alb.
	12/19/10	Some fever, drowsy.....	.....
18—W., aged 66... Surg. No. 26508	9/7/10	Hypertrophy of prostate; myocarditis.....	Alb. +; pus.
	9/17/10	Catheter drainage	Alb. +; pus.
	10/1/10	Catheter drainage	Alb. +; pus.
19—L., aged 57...	10/7/10	Carcinoma of prostate; pyuria.....	Alb. +
	10/17/10	.....	.....
	10/21/10	.....	.....
20—P. L., aged 69. 26236	7/19/10	Hypertrophy of prostate; acute retention; good condition.	Pyuria.
21—R., aged 69... Surg. No. 25637	3/24/10	Hypertrophy of prostate; retrovesical abscess; septic temperature; fracture hip; bad shape.	Pyuria.
	3/31/10	.....	.....
	4/12/10	Very sick; suprapubic drainage.....	.....
	4/23/10	.....	.....

* Left kidney excreted 44 per cent. in 1 hour and 10 minutes; right kidney trace.

TABLE 12.—AUTOPSY

Time of Appearance (min.)	Percentage of Drug		Remarks
	One Hour.	Two Hours.	
..	....	39.5	Died 4/10/11. Autopsy: Arteriosclerosis, myocarditis, acute mitral and tricuspid endocarditis, acute and moderate chronic diffuse nephritis; acute nephritis of only a few days' duration.
..	....	43.5	Died 4/8/11, of cerebral embolus. Autopsy 3533: Ulcerative aortic endocarditis, acute vegetative endocarditis left auricle; cardiac dilatation and hypertrophy, chronic passive congestion of viscera.
..	....	15.5	Autopsy 3461: Atrophy of right kidney from old thrombosis of renal artery; left kidney shows chronic diffuse nephritis; small, granular kidney.
..	....	32.2	Autopsy: Moderate grade of chronic diffuse nephritis.
24	33.0	68.0	Died of pneumonia ten days later; no operation. Autopsy: Well-developed double polycystic kidneys.
..	2.9	6.2	Died 11/16/10, in coma. Autopsy: Severe amyloid nephritis.
..	....	Trace.	
..	0.0	0.0	Died 11/14/10. Autopsy: Small granular kidneys, superimposed acute nephritis.
..	0.0	0.0	1/11/11, double nephrotomy; died in twenty-four hours; both kidneys filled with calculi, being mere thin-walled pus sacs.
..	....	Trace.	
..	....	5.5	
..	....	Faint trace.	
30	24.4	49.0	Prostatectomy 2/4/10; died twelve hours after operation, of heart failure; ether anesthesia.
16	31.0	42.8	Autopsy: Some myocarditis and arteriosclerosis, slight chronic nephritis, slight dilatation of pelves; discrete scattered areas of acute pyelonephritis.
17	8.8	33.8	
40	....	Trace.	Went into coma 1/18/10 and died 1/19/10.
30	....	Trace.	Autopsy: Some dilatation of pelves, which were filled with pus; marked grades of interstitial nephritis, kidneys being ⅓ normal size; some diffuse pyelonephritis.
23	....	Trace.	
..	....	57.0	Autopsy 3499: Fatty degeneration of viscera, including kidneys.
..	....	6.0	Died in uremia 4/9/11.
..	....	3.0	Autopsy: Extreme grade of chronic interstitial nephritis; cortex almost destroyed; superimposed acute nephritis (?).
..	....	16.1	Died from heart condition, 4/20/11. Autopsy: Myocarditis, pericarditis; kidneys show arteriosclerotic scars with a mild chronic diffuse nephritis and a marked chronic glomular nephritis.
..	....	26.6	Died 1/21/11. Autopsy 3494: Chronic and acute mitral and aortic myocarditis, marked cardiac dilatation, acute and moderate chronic diffuse nephritis.
8	•	....	Nephrectomy and right kidney found almost entirely destroyed; died four days later, of hemorrhage; autopsy showed a large hypertrophied kidney with microscopically some very slight chronic nephritis.
30	6.0	16.0	Died two weeks after test. Autopsy: Dilatation of both renal pelves and marked grade of chronic bilateral pyelonephritis.
8	18.5	43.5	Died ten days after last test, in uremia.
23	8.0	13.0	Autopsy 3488: Old chronic pyonephrosis of left kidney; right kidney hypertrophied but showing chronic diffuse nephritis and a marked diffuse acute pyelonephritis.
15	16.0	31.2	Prostatectomy successful; two weeks after operation myocarditis became aggravated, uremia developed, ending in death.
..	25.0	38.0	
..	18.0	30.5	Autopsy 3474: Infantile right kidney; left kidney showed chronic diffuse nephritis.
25	Trace.	7.1	Prostatectomy under gas anesthesia; did well for ten days; became constipated, uremia developed and died some days later.
40	7.0	12.5	
25	5.6	12.0	Autopsy 3466: Acute ureteritis and pyelitis; chronic diffuse nephritis of severe grade.
15	15.1	29.3	Died on third day following prostatectomy, from cerebral hemorrhage. Autopsy: Kidneys show an arteriosclerotic form of nephritis.
14	13.8	33.8	Died 4/25/10. Autopsy: Chronic myocarditis, arteriosclerosis; chronic cystitis, hypertrophy of prostate, retrovesical abscess; kidneys showed some chronic diffuse nephritis with marked epithelial necrosis, the latter being, of course, a terminal occurrence.
13	25.5	58.0	
30	15.0	40.0	
13	16.6	45.2	

the tuberculous focus was probably small and confined, so that the remaining healthy portion probably underwent compensatory hypertrophy.

COMPARISON OF PHTHALEIN EXCRETION WITH AUTOPSY FINDINGS

An opportunity was afforded in twenty-one cases (see Table 12) of comparing the phthalein excretion with the pathological condition of the kidneys at autopsy.

In the cases in which the phthalein excretion was moderately decreased the kidneys showed moderate pathological changes. In those cases in which no phthalein was excreted, or only a small amount, extensive and severe renal destruction was invariably found.

In one heart case (No. 14, Table 12) showing an excretion of 43.5 per cent. for two hours, which is a definite but moderate reduction, only a passive congestion was found. That this condition can interfere with function other clinical cases seem to confirm.

In one case double polycystic kidneys were encountered, although the phthalein excretion was normal. The patient exhibited no symptoms from this condition during life, death being due to pneumonia. The fact that polycystic kidneys may be present for a great many years without symptoms and also that they are usually unexpectedly discovered at autopsy in patients dying from other conditions is good proof of their functional efficiency.

CONCLUSIONS

1. The absorption of phenolsulphonephthalein following injection into the lumbar muscles is better than the absorption from the gluteal injection, while the latter is superior to subcutaneous injection.

2. Administration into the lumbar muscles is the method of choice.

3. Experimentally those diuretics that stimulate the renal cells to increased activity cause some increased secretion of phenolsulphonephthalein, while those that act mechanically produce no increased secretion. Clinically diuretics do not influence the phthalein output.

4. Experimental evidence seems to indicate that phenolsulphonephthalein is excreted mostly by the tubules but probably also to a slight extent by the glomeruli.

5. The renal cells display a striking specificity in the excretion of phenolsulphonephthalein.

6. The phenolsulphonephthalein as used by us has many advantages over all other functional tests so far proposed.

7. It is better adapted for use as a functional test than any other drug previously employed for the same purpose, on account of its early appearance in the urine and the rapidity and completeness of its elimination by the kidney and the reliance to be placed on its findings.

8. The method of quantitative estimation of the amount of drug excreted is simple and exceedingly accurate.

9. It is of immense value from a diagnostic and prognostic standpoint in nephritis inasmuch as it reveals the degree of functional derangement in nephritis whether of the acute or chronic variety.

10. In the cardiorenal cases so far studied the test has proved of value in determining to what degree renal insufficiency was responsible for the clinical picture presented.

11. The test has proved of value not only in diagnosing uremia from conditions simulating it, but has also successfully indicated that uremia was impending when no clinical evidence of its existence at the time was present.

12. The test has proved of great value in revealing the true renal condition in cases of urinary obstruction. It is here of more value than the urinary output, total solids, urea or total nitrogen, and enables the surgeon to select a time for operation when the kidneys are in their most favorable functional condition. The improvement in the renal condition in cases of urinary obstruction following the institution of preliminary treatment is strikingly indicated by this test.

13. In unilateral and bilateral kidney diseases the absolute amount of work done by each kidney as well as the relative proportion can be determined when the urines are obtained separately.

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